Side Effects of Medical Cancer Therapy

Prevention and Treatment

Mario A. Dicato
Eric Van Cutsem
Editors

Second Edition

Springer

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ISBN 978-3-319-70252-0 ISBN 978-3-319-70253-7 (eBook)
https://doi.org/10.1007/978-3-319-70253-7

Library of Congress Control Number: 2018940897

Preface to the First Edition

The reason for publishing a book on side effects of drugs used in oncology is the fact that numerous new drugs, mostly classified as "targeted therapy," have different and very varied spectra of side effects. As standard chemotherapy drugs have not changed much over the years in their adverse effect profiles, oncologists are usually very familiar with these problems, especially because over the past 20 years only a few new chemotherapeutic drugs have been marketed.

Another aspect of oncology that has changed over the past two decades is the fact that with the increase in life expectancy, the median age at diagnosis of cancer has increased and is presently around 70 years. Therefore, comorbidities have become routine in oncological services, and many patients are being treated with multiple medications for other pathologies, which multiplies drug interactions and compliance problems.

Targeted drugs have flooded the oncological literature, and their spectrum of side effects is increasing, especially since additional drugs become available every year and are being used in several malignancies. This change of spectrum of side effects is less and less organ-limited, and a physician specialized in, for example, gastrointestinal malignancies is now confronted with cardiac (trastuzumab in gastric cancer) or dermatologic (EGFR inhibitor in colorectal cancer) toxicity. Hence, in order to make it easy to look up a problem, overlaps are unavoidable.

In putting together the layout of a book on side effects of medical cancer therapy, several problems arose. Should the side effects be grouped by organ, by drug, by type of toxicity, or by other factors? A compromise needed to be found. Therefore, the majority of the book is organ-oriented, with the exception of chapters on pharmacogenetic-pharmacokinetic, cardiac, dermatologic, and supportive care aspects.

I am grateful to the authors who spontaneously accepted the task of writing their respective chapters. Though most of them are prominent in their fields, many realized only later that more than an update of a previously studied topic was required and that they had to start anew. I thank them for complying.

Special thanks to Diane Lamsback from Springer for her untiring help in the preparation of this book.

Luxembourg, Luxembourg — Mario A. Dicato

Preface to the Second Edition

The reason to publish the first edition of this book was motivated by the fact that over a relatively short period of time a new non-chemotherapy type of oncology drugs became available with a completely different spectrum of side effects.

Now 4 years after the first edition the number of these drugs has continued to increase considerably. From January 2009 to December 31, 2013, the FDA approved 51 drugs for 63 indications (doi: 10.1001/jamaoncol.2015.0373) and from January 2014 to April 2017 about 45 new drugs have been approved (FDA Approved Drugs for Oncology www.centerwatch.com), so the time has come for an update of this field.

Immuno-oncology has evolved into an impressive field of cancer therapy and a chapter on this topic is added to this new edition.

We appreciate all the authors for reviewing and updating their chapters, not an easy task with the rapid availability of all these new drugs and their side effects.

We are grateful to Evgenia Koutsouki and Rekha Udaiyar from Springer-UK for their patience and untiring help for the practical aspects in putting this book together.

Luxembourg, Luxembourg — Mario A. Dicato
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Drug Interactions and Pharmacogenetics

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François Lokiec

Abstract

Drug interaction in cancer chemotherapy is one of the most common phenomena in cancer treatment. Cancer patients often take several medications at the same time, not only for treating their cancer but also for side effects and other secondary illnesses. The number of comedications increases with age, and drug interactions are critical for elderly patients. Because of this, they can be at high risk for adverse drug interactions and duplicate medications. Consequences of these interactions can range from inactivation of cancer-fighting medications to severe injury or death of the patient. Pharmacogenetics studies the relationship between genetic polymorphisms and individual responses to drugs. In recent years, there has been great progress in our knowledge of the effects of drug-metabolizing enzymes and molecular target genetic polymorphisms on cancer chemotherapy. Pharmacogenetics focuses on the prediction of drug efficacy and toxicity based on a patient's genetic profile with routinely applicable genetic tests to select the most appropriate medication at optimal doses for each individual patient.

Keywords

Anticancer drugs · Drug interactions · Pharmacogenetics · Pharmacodynamics Pharmacokinetics · Cytochromes P450

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M. A. Dicato, E. Van Cutsem (eds.), *Side Effects of Medical Cancer Therapy*,
https://doi.org/10.1007/978-3-319-70253-7_1

1.1 Introduction

Drug interactions and pharmacogenetics seem to present two different problems for the side effects of cancer chemotherapy. In fact, we will see later in this chapter that these two approaches are not so different.

Drug interaction in cancer chemotherapy is one of the most common phenomena in cancer treatment. Drug interactions in oncology are of particular importance owing to the narrow therapeutic index and the inherent toxicity of anticancer agents. Interactions with other medications can cause small changes in the pharmacokinetics or pharmacodynamics of a chemotherapy agent that could significantly alter its efficacy or toxicity. Evaluation of drug potential interactions should not be limited solely to the anticancer group. A drug interaction occurs whenever the effects of one drug are modified by the prior or concurrent administration of another pharmacologically active substance. Such interactions may result in an antagonistic, synergistic, or unexpected response [1].

A drug interaction is defined as the pharmacologic or clinical response to the administration or co-exposure of a drug with another substance that modifies the patient's response to the drug. It is reported that more than 20% of all adverse reactions to drugs are caused by interactions between drugs [2]. This incidence increases among the elderly and patients who take two or more medications. Patients with cancer are particularly at risk for drug interactions because they could be taking many different medications as part of their cancer treatment or for the management of other illnesses [3].

Drug interactions can occur throughout the process of drug disposition as a result of endogenous and exogenous factors. Drug interactions can be the result of pharmacokinetic or pharmacodynamic factors or a combination of mechanisms. Pharmacokinetic interactions involve one drug or substance altering the absorption, distribution, metabolism, or elimination of another drug or substance. A common example of a pharmacokinetic interaction occurs when two drugs compete for the same metabolic pathway. When the pathway becomes saturated, neither drug can be metabolized fully, which results in higher serum concentrations of the agents and can lead to clinically unfavorable consequences. Pharmacodynamic interactions occur when two drugs or substances have similar molecular targets but do not affect the pharmacokinetic parameters of each other. When two or more drugs that have similar pharmacodynamic activity are coadministered, the additive effects might result in an excessive response or toxicity. Pharmacodynamic interactions between drugs with opposing effects can reduce the response to one or both drugs [4–6].

In this section, we have intentionally focused on the unexpected drug interactions that have been well documented in cancer patients. A special section describes interactions between anticancer drugs and resistance-modifying agents because although pharmacodynamic interactions are the aim of this kind of association, pharmacokinetic interactions can be the chief explanation for resistance reversal.

1.2 Principles of Drug Interactions

1.2.1 Physical Interactions or Chemical Incompatibilities

Cancer patients usually receive intravenous (IV) anticancer drugs plus other supportive treatment, such as antiemetics, antibiotics, and others. Special attention should be paid to the physical and chemical interactions that can occur when the drugs are given simultaneously [7].

Cancer patients usually require multiple-drug therapy. In fact, the cancer chemotherapy regimen alone often consists of three or four agents. Supportive therapy adds more drugs to the overall regimen, resulting in the (perceived) need to administer several drugs simultaneously. Also, having a steep dose–response curve, low therapeutic index, and significant toxicity, anticancer agents are particularly critical drugs. Any deviation from the dose or concentration that produces optimum activity is bound to cause problems one way or another, either through increased toxicity or loss of response. Either way the outcome may be fatal for the patient. Furthermore, one should keep in mind that chemical inactivation of anticancer drugs by the admixture of other drugs is not usually visible in terms of evident product degradation. In other words, even if an added drug does not cause clouding, precipitation, or a color change in the cytotoxic drug solution, you can never be sure that there will be no chemical inactivation. So make it a rule to always administer cytotoxic drugs alone [8].

Selected examples are presented in the following sections.

1.2.1.1 pH Effects

Some cytotoxic drugs (e.g., fluorouracil) dissolve only at extreme pH values. Adding other drugs may cause such a shift in pH that fluorouracil will flocculate.

1.2.1.2 Solubilizers

Other cytotoxic agents can be kept in solution only with the aid of solubilizers, which tend to be effective only within specific concentration ranges. Outside these ranges, the drugs may crystallize (e.g., etoposide, teniposide, paclitaxel).

1.2.1.3 Plasticizers

Solubilizers may leach plasticizers from plastics, thus producing toxic effects (this is why PVC-free transfusion-giving sets must be used for paclitaxel infusions). Conversely, lipophilic cytotoxic drugs may be extracted by plasticizers from an aqueous solution.

1.2.1.4 Sorption

Protein sorption to glass surfaces has been described in the literature. This phenomenon may cause loss of activity of biologically potent drugs, which tend to be administered in minute amounts.

1.2.2 Chemical Reactions

Of the broad spectrum of possible chemical reactions, here are a few examples:

- Hydrolysis (e.g., etoposide lactone ring cleavage in basic pH range)
- Redox reactions (e.g., platinum coordination complexes and sulfite, thiols)
- Photolysis (e.g., carmustine [nitrosourea] or dacarbazine [triazene])
- Racemization (e.g., etoposide as CH-acid compound in alkaline solution)
- Formation of coordination complexes (e.g., platinum derivatives)

1.2.3 Denaturation

Many proteins are stable only at specific pH values and ionic strengths (filgrastim, for instance, is unstable in normal saline). Deviations may lead to denaturation, which will not necessarily be visible as flocculation in the case of biologically potent drugs (growth factors, interferon). Loss of biologic activity will then not be macroscopically evident.

1.2.4 Pharmacokinetic Interactions

Very few cytotoxic agents are administered by the oral route, but now with the tyrosine kinase inhibitor family, everything has changed; all the "small molecules" are orally administered. We should, therefore, take the pharmacokinetic interactions into consideration, including the absorption, distribution, metabolism, and elimination of anticancer drugs.

1.2.4.1 Absorption

Many factors are able to reduce the digestive absorption of a drug. These include the degree of ionization of the drug, its contact with the digestive mucous (transit problems, defective digestive secretion), the gastric emptying, and gastrointestinal motility. Food delays gastric emptying, raises intestinal pH, increases hepatic blood flow, and slows gastrointestinal transit, so it can significantly affect the pharmacokinetic profile of some orally administered medications. Food–drug interactions can have four pharmacokinetic effects on the bioavailability of the orally administered anticancer agent: delayed, decreased, increased, or unaffected absorption.

Some orally administered anticancer agents are prodrugs, which require metabolic activation for cytotoxic activity through first-pass effects in the gastrointestinal tract and/or liver before they reach the systemic circulation. Capecitabine, altretamine, etoposide phosphate, and estramustine phosphate sodium are anticancer agents that are used in the treatment of various solid tumors (including breast, colorectal, ovarian, lung, prostate, and testicular cancer) and require such activation. Therefore, factors that alter the absorption of these medications can have profound effects on their pharmacokinetics. A decrease in the rate and extent of absorption is

noted when estramustine phosphate sodium is given with food or milk, and bioavailability has been reported to decrease by 36 and 63%, respectively [9]. Therefore, it is recommended that estramustine phosphate sodium be taken with water 1 h before or 2 h after a meal. By contrast, food has been shown to have only a minor effect on the pharmacokinetics of fluorouracil (5-FU). The rate of absorption of capecitabine (a 5-FU prodrug) is decreased in a fed state, which results in an increase in hepatic first-pass metabolism, which in turn reduces the extent of systemic absorption of the prodrug [10]. However, a greater effect is seen on the area under the concentration–time curve (AUC) of capecitabine as compared with 5′-deoxy-5′ fluorouridine (5′-DFUR), the precursor to the pharmacologically active compound 5-FU. So, the change in AUC of capecitabine is probably not clinically significant, as capecitabine itself is not the active compound.

The absorption of orally administered anticancer agents that are not prodrugs can also be altered by metabolism within the gastrointestinal tract [11]. Evidence indicates that the activity of cytochrome P450 enzymes (CYP enzymes) in the gut wall is a significant factor that alters the bioavailability of orally administered anticancer agents that are CYP3A substrates [12]. Drug–food, drug–herb, or drug–drug interactions can occur when an orally administered CYP3A substrate is given concomitantly with an inhibitor or inducer of intestinal CYP activity. One of the best described examples of a food that alters intestinal CYP3A activity is grapefruit juice. Grapefruit juice is known to be a potent inhibitor of intestinal CYP3A4 and therefore increases the bioavailability of various drugs, such as the anti-inflammatory and immunosuppressive agent cyclosporine and the calcium-channel blocker nifedipine [13–16].

1.2.4.2 Ionization

Digestive absorption is complete when it is achieved by passive diffusion (e.g., in a non-ionized form). Most of the substances that are capable of ionizing a drug decrease its digestive absorption. Substances such as alkalinizing agents decrease the absorption of acid drugs, and acidifying drugs (citric and tartaric acid) decrease the alkaline drug absorption.

1.2.5 Complexation

This type of interaction occurs during the digestive process, when the drug forms (with another drug or any other substance) a nonresorbable complex (e.g., aluminum colloids combined with acid drugs).

1.2.5.1 Contact with the Digestive Mucosa

This kind of antagonism includes different physiopathologic circumstances, such as food attendance and lack of digestive secretion.

1.2.5.2 Gastrointestinal Motility

Drugs are mainly absorbed at the intestinal level, where a wide mucous surface exists. Absorption at this level is affected all the more when gastric emptying is faster. Any

substance that modifies the gastric emptying acts on the kinetics of the intestinal absorption of anticancer drugs. The anticholinergic substances slow down gastric emptying and delay the absorption of the drugs. On the other hand, metoclopramide accelerates gastric emptying and accelerates the absorption of associated drugs.

Modifications in Drug Diffusion

These modifications become apparent in either an increase in the concentration of the free active form of the drug or a decrease in this concentration.

1.2.6 Binding to Plasma Proteins

The competition of drugs for plasma proteins is one of the most common reasons for the occurrence of toxic side effects (methotrexate–aspirin [17, 18], methotrexate–indomethacin [19], methotrexate–trimethoprim–sulfamethoxazole [20, 21], etc.). Clinicians should be very careful with the association of drugs that are highly bound to proteins (usually albumin) because the binding sites are the same and limited in number.

1.2.6.1 Modification of the Tissue Binding

This modification is the result of competition between two drugs for the same binding sites in a tissue. This kind of interaction is similar to the protein plasma binding but directly into the tissues.

Metabolic Interactions

The metabolic interactions mainly occur with drugs with hepatic metabolism. The anticancer drugs involved in metabolic interactions with other drugs are those metabolized by liver enzymes, which are induced or inhibited by the associated substances. The main metabolic inducers are rifampicin, spironolactone, and phenobarbital [22, 23]; the main metabolic inhibitors are monoamine oxidase inhibitors, tricyclic antidepressants, phenothiazine neuroleptics, and allopurinol [24, 25].

Modifications in the Elimination

Drug interactions leading to changes in the elimination of anticancer drugs mainly concern urinary drug elimination. Modifications in urinary elimination are principally due to changes of the urine pH expressing a modification in the ionization of the substances filtered by the glomerulus and secreted at the proximal tubule level. An increase in the degree of ionization of the drug corresponds to an increase in the urinary elimination of the drug. On the other hand, a decrease in drug ionization leads to a decrease in its renal elimination.

Miscellaneous

We should always take into account the possibility that the patient is suffering from another disorder that could, by itself, interact with the pharmacokinetic behavior of the anticancer drug. For example, thyroid dysfunction may influence drug pharmacokinetics, just as the cardiovascular and respiratory systems can.

1.2.7 Pharmacodynamic Interactions

Pharmacodynamic interactions involve the therapeutic power of the anticancer drug. They can enhance or decrease antineoplastic efficacy and modify the importance of the drug's toxic side effects. Pharmacodynamic interactions mainly concern the hematologic system, the liver, and the kidney.

1.2.7.1 Terminology

The anticancer drug alone is considered as reference for the therapeutic activity. The pharmacologic consequences of drug interactions are always quantitative modifications of one or more effects of the associated drugs. Either the intensity of an effect, its duration, or both can be affected. If it is a global increase of the effect, the interaction is either synergy or enhancement. If it is a decrease of the effect, the interaction is antagonism.

1.2.7.2 Synergy and Antagonism

Usually, we use the term "synergy" when two drugs have effects going in the same direction. The effect is additive when the observed effect is the sum of both effects. Synergy's main characteristic is that it affects only the common effects of the drugs. According to the extent of the modifications that occur, it can be described as partial, additive (the most frequent), and synergistic. Conversely, antagonisms can be observed when the effects of drug association produce a milder effect than the most active drug alone. The antagonism can be total or partial.

1.2.7.3 Enhancement and Antagonism

Enhancement is characterized by a special phenomenon in which the increased effects all belong to the same drug. Other substances in the association do not have these effects but are capable of increasing their intensity when associated with the drug. Antagonism also exists in such situations.

It is important to note that the term "antagonism" is used to describe two phenomena, which are the contrary of synergy and the contrary of enhancement. Usually, interaction between two drugs is not defined by its mechanism but rather by its pharmacologic consequences. The interaction supervention supposes that the interaction is sufficiently intense to have a clinical translation.

It is relatively common to detect drug interactions in pharmacokinetic terms with no pharmacodynamic repercussions.

1.3 Interactions Between Anticancer Drugs and Other Active Substances

Very little study has been devoted to interactions between anticancer drugs and other active substances, which is quite surprising because cancer patients usually receive a large number of pharmaceuticals and the therapeutic margin for anticancer drugs is always narrow. Mostly, the drug interactions have been reported case by case (Tables 1.1 and 1.2).

Table 1.1 Examples of drug–drug interactions between anticancer drugs and other active substances

Other active substances	Examples of interactions	References
Antiemetics	Metoclopramide might enhance the cisplatin and the epirubicin toxicity	[26, 27]
Antiulcer drugs	Cimetidine increases cyclophosphamide, nitrosoureas, doxorubicin toxicities	[28–30]
NSAIDs	NSAIDs block the elimination of MTX through renal tubular secretion, leading to increase of MTX blood levels and toxicities	[31–34]
Antimicrobial agents	Penicillin delays MTX excretion	[35]
Anticoagulants	Warfarin has been reported to be synergistic with 5-FU	[36]
Psychiatric drugs	Benzodiazepines act on many anticancer drugs	[37–40]

Table 1.2 Examples of drug–drug interactions between MTX and other anticancer drugs

Other active substances	Examples of interactions	References
Penicillin	Delay of MTX excretion	[35, 41, 42]
Salicylates	Displacement of protein binding and increased MTX toxicity	[17, 18]
NSAIDs	Decrease elimination of MTX and increased toxicity	[31–34]

1.3.1 Antiemetics

Many anticancer drugs induce nausea and vomiting in cancer patients. For these reasons, antiemetics are usually used in combination with cancer treatments. The antiemetic drugs usually act at the level of the central nervous system through the dopamine or serotonin receptors. Among the antiemetics, chlorpromazine and metoclopramide seem to be the most involved in drug interactions.

1.3.1.1 Chlorpromazine

Chlorpromazine combined with caffeine enhances cytotoxicity of alkylating agents in some rodent transplantation tumors and in the human melanoma xenograft system in mice [43]. The mechanism of its action may be related to increased retention within the tumor cells, to fixation of DNA damage, or to a nonspecific cytotoxicity. On the other hand, when chlorpromazine and caffeine have been used in patients with disseminated malignant carcinoma, no tumor cytotoxicity was enhanced [44].

1.3.1.2 Metoclopramide

Metoclopramide might enhance antitumor activity of anticancer drugs because structurally related compounds (nicotinamide, benzamide, etc.) inhibit the chromatin-bound enzyme adenosine diphosphate ribosyl transferase [26]. This enzyme is activated by DNA-damaging agents and may play a role in DNA repair. This hypothesis was tested against a squamous cell carcinoma of the head and neck

in xenografted nude mice. Metoclopramide was given at the same time as cisplatin and again 24 and 48 h later. Compared with mice not given metoclopramide, cisplatin antitumor activity was doubled, with no other increase in cisplatin toxicity. In another study with metoclopramide and chlorpromazine, epirubicin cytotoxic activity was enhanced when tested against Chinese hamster fibroblasts without any intrinsic cytotoxic activity [27].

1.3.1.3 Granisetron and Ondansetron

Development of serotonin receptor antagonists gives a therapeutic class without the classic adverse reactions associated with dopamine receptor blockade, such as severe sedation or extrapyramidal side effects. Finally, of the selective 5HT3 receptor antagonists, both granisetron and ondansetron have been tested for their potential to affect drug cytotoxicity. No evidence was found that these two compounds antagonize or enhance the antitumor properties of anticancer drugs such as cisplatinum [45, 46].

1.3.2 Antiulcer Drugs

Cimetidine and ranitidine are histamine H2 antagonists used for the treatment of diseases caused by gastric hyperacidity. Evidence has accumulated that cimetidine can alter drug metabolism through the ability to inhibit the hepatic microsomal cytochrome P450 enzyme system [47]. Ranitidine binds less avidly to microsomal enzymes and, in clinical dosage, does not appear to significantly alter microsomal metabolism [47]. Ranitidine when associated with cyclophosphamide does not change the pattern or degree of cyclophosphamide-induced leukopenia or granulocytopenia. Ranitidine administration has no significant effect on the area under the curve values for the two major oncolytic cyclophosphamide metabolites 4-hydroxycyclophosphamide and phosphoramide mustard; nevertheless, ranitidine administration is associated with significantly prolonged plasma terminal half-life and increases area under the curve for the parent drug that is not active [48].

Several anticancer drugs, including cyclophosphamide, the nitrosoureas, doxorubicin, procarbazine, and hexamethylmelamine, undergo metabolism through the hepatic oxidative microsomal enzyme system [28–30].

The result of the interaction between cimetidine and the former anticancer agents is a decrease of the antineoplastic agent clearance, leading to an increase in their activities and toxicities by typical pharmacokinetic interaction [49–51].

1.3.3 Analgesics (Nonsteroidal Anti-inflammatory Drugs)

Many cases of drug interactions between nonsteroidal anti-inflammatory drugs (NSAIDs) and anticancer drugs have been reported. There have been fatal interactions between methotrexate and naproxen [52] as well as clinical and pharmacokinetic evidence of life-threatening interactions between methotrexate and ketoprofen [31]. In the latter chapter, no abnormalities in methotrexate kinetics or toxicity were

noticed when ketoprofen was given at least 12 h after completion of high-dose methotrexate. The kidney was suggested to be the site of drug interaction.

A probable interaction between methotrexate and/or 5-FU and indomethacin has been reported [32]. This NSAID is known to enhance cell killing by methotrexate in vitro. Other mechanisms than renal damage are of importance in the explanation of indomethacin–methotrexate interaction such as displacement and increased transport into malignant cells [33]. Inhibition of prostaglandin synthesis seems to participate in the effect of indomethacin on methotrexate cytotoxicity.

Pharmacokinetic interaction between cisplatinum and indomethacin has been reported in vitro and in vivo [34]. The result of this interaction was an increase in free cisplatinum concentrations due to the fact that both indomethacin and cisplatinum are highly protein-bound.

Morphine, cocaine, and atropine stimulated transport of choline and nitrogen mustard into L5178Y lymphoblasts [53] and into leukemic white blood cells [54], which is interesting since the accumulation of alkylating agents is of importance for their cytotoxicity.

1.3.4 Antimicrobial Agents

Antimicrobial therapy is quite common for patients treated for hematologic malignancies or solid tumors. For this reason, extensive studies have been published on the effects of anticancer agents on the antibacterial activity of antibiotics [55]. However, the effects of antibiotics on the antineoplastic activity of anticancer drugs have been considerably less discussed.

Nevertheless, there are some reports on the effects of antibiotics on the toxicity of anticancer drugs. Penicillin in combination with furosemide impaired methotrexate renal secretion and caused increased toxicity [41]. Penicillin also inhibits accumulation of methotrexate in renal slices of rabbit and monkeys and delayed the elimination of methotrexate [35]. Decreased methotrexate antitumor effect has been reported with kanamycin, neomycin, and penicillin due to a decrease of the cellular uptake of methotrexate [42]. The nephrotoxic antibiotics aminoglycoside gentamicin can enhance the toxic renal effects of methotrexate on the tubule [56].

Trimethoprim–sulfamethoxazole and netilmicin enhance the epirubicin oxygen radical formation.

Antifungal drugs such as amphotericin B potentialize the cytotoxicity of many anticancer agents (doxorubicin, vincristine, CCNU) on leukemia cells of mice [57]. Amphotericin B has also been suggested to potentialize the effect of doxorubicin, cyclophosphamide, and carmustine in human neoplasia [58].

1.3.5 Miscellaneous

Anticoagulants such as dicumarol increase the enzymatic activation of mitomycin C to reactive alkylating metabolites and cause a subsequent increased cytotoxicity

[59]. Warfarin, another anticoagulant, retards the growth of Lewis lung carcinoma in mice and small cell carcinoma of the lung in humans [60]. A synergistic action between 5-FU and warfarin has been also reported [36].

Psychiatric drugs are quite widely used in elderly patients being treated for cancer. The use of these psychopharmaceuticals has an influence on the activity of the antineoplastic agents. Diazepam blocks the cells in pre-S-phase and induces mitotic arrests at prometaphase by inhibiting centriolar separation [37, 38]. Diazepam also causes an enhancement of doxorubicin and mitoxantrone cytotoxicity [39]. Amitriptyline, a tricyclic antidepressive, modifies the blood–brain barrier and enhances the penetration of drugs into the central nervous system [40].

Bronchodilators are often indicted in patients with airway obstruction or prominent wheezing. The main classes of bronchodilators, (beta)β-adrenoceptor agonists, and methylxanthines raise the level of 3′ 5′ cyclic AMP in mast cells and bronchial smooth muscles, thereby inhibiting mediator production and reducing muscle contractility.

As cyclic AMP is a second messenger in other cellular events, it is evident that bronchodilators might influence tumor cells and interact with cancer treatment [61]. The interaction of cyclic AMP on the cytotoxic effect of doxorubicin has been suggested [62].

1.4 Anticancer Drug–Anticancer Drug Interactions

The interactions among anticancer drugs are of importance because the chemotherapeutic protocols include at least three different antineoplastic drugs. This is why the possibility of drug interactions should be known and taken into account. Two aspects of drug interactions are concerned. Drug interaction may be desired for clinical modulation of an anticancer agent or undesired.

1.4.1 Modulation

The modulation of an anticancer agent is accomplished by a compound that modifies some aspect of the biochemical pharmacology of the anticancer drug to improve its therapeutic index. The best example of clinical anticancer drug modulation is that of 5-FU modulation by leucovorin, which is discussed in another chapter of this book.

Another example of 5-FU modulation is the combination of methotrexate (MTX) and 5-FU [63]. The interaction of MTX and 5-FU is complex, and theoretical models for both antagonism and synergy have been postulated. By altering reduced folate pools involved in ternary complex formation, MTX may be expected to hinder 5-FU inhibition of thymidylate synthase [64, 65]. By inhibiting de novo purine synthesis, there is also less nucleic acid synthesis available for fluoropyrimidine nucleotide incorporation. However, the net balance of potential negative and positive effects appears to favor synergy. The most plausible mechanism of MTX/5-FU

interaction appears to be through increased levels of phosphoribosylpyrophosphate, an intermediate needed in de novo purine synthesis, resulting from inhibition of purine synthesis [66].

1.4.2 Undesired Drug Interactions

The undesired anticancer drug–anticancer drug interactions are probably fairly frequent because more than 800 polychemotherapeutic protocols have been recorded (hematologic malignancies plus solid tumors). In theory, it would seem to be an impossible task in a limited space to develop the subject of drug interactions when anticancer drugs are combined, but this is not the case in practice. In fact, very few interactions among the anticancer drug group have been reported in the literature. For this reason, it is more important to give the philosophical criteria for planning a polychemotherapeutic protocol.

In order to obtain a better antitumor response with drug association than with each drug alone, an association should discriminate between tumor sensitivity and toxic side effects. In other words, a drug association should combine the antineoplastic properties of each drug without adding their toxic side effects. One of the fundamental principles of drug combination is to combine drugs that do not have the same toxic effects.

Some impossible associations due to the same toxic effects, such as methotrexate with cisplatinum for renal toxicity, have led to second-generation drugs that do not have the same toxicities. For example, carboplatin and trimetrexate are free of the renal toxic effect of their corresponding first-generation drugs, due to the fact that the association of cisplatin with trimetrexate [67] and carboplatin with methotrexate [68] is possible and safer.

1.5 Drug Interactions Between Anticancer Drugs and Resistance-Modifying Agents

Several systems exist by which tumor cells resist cancer chemotherapy. Numerous resistance-modifying agents are used in clinics in order to circumvent multidrug resistance (MDR), which is one of the most frequent reasons for chemotherapy failure. To reverse MDR, the combination between anticancer agents and resistance-modifying agents leads to pharmacologic interactions [69].

Pharmacodynamic interactions could be defined as desirable interactions, but the question is as follows: Are the pharmacodynamic direct interactions in target organs or are they due to pharmacokinetic modifications of the anticancer agent? In other words, the maximum tolerated dose of the antineoplastic agents when administered without the modulator is usually well established, but this is not the case for the maximum tolerated dose of the anticancer drugs when associated with the MDR-modulating drug. Clinicians should be very careful when they initiate a protocol that associates anticancer chemotherapy and MDR modulators.

1.6 Pharmacogenetics

Pharmacogenetics relates variation in gene structure to variation in phenotypes associated with therapeutic or toxic responses to drugs and other foreign chemicals in human populations [70]. Methods of study in pharmacogenetics include the correlation of observed variation in drug pharmacokinetics or pharmacodynamics with allelic variation in individual genes encoding proteins that act as targets of drug action or mediators of drug elimination, the elucidation of biochemical and molecular mechanisms that produce variable protein function, the development of probe drug-testing procedures and predictive animal models to more precisely define the role of genetics in producing variable drug response in human populations, and the development of simple genetic tests to predict unexpected drug responses and thus to guide the clinician in the selection of appropriate drugs and drug doses [71–73].

Personalized medication management, including DNA testing, is extremely important for the proper treatment of cancer because finding the right drug and dose is so vitally important. This is not surprising to people that study genetics. Research shows that of all the clinical factors that alter a patient's response to drugs, such as age, sex, weight, general health, and liver function, genetic factors account for a significant proportion [74–76].

Early in the development of irinotecan, researchers observed that the active metabolite of the drug, SN-38, was cleared from the body through a process called glucuronidation [77]. A gene called UGT1A1 was responsible for sticking that glucuronide group onto the drug [78, 79]. Once glucuronide was on a compound, it was easily excreted by the bile. So, for example, bilirubin and a number of estrogen molecules in the body are glucuronidated. Irinotecan is one of several anticancer drugs that also undergo this process. Researchers found that a subset of the population, about 10%, has a genetic change in the UGT1A1 gene that hinders their ability to perform this glucuronidation process [80]. This change does not have an apparent phenotype; it is something that could be detected by the usual bilirubin test or by some outward manifestation of the patient. When patients with the genetic change in UGT1A1, called UGT1A1*28, receive a standard dose of irinotecan, they have a very high risk of severe or even fatal neutropenia, a condition that drastically lowers the ability of the body to fight off infection. This UGT1A1*28 genetic change is responsible for Gilbert's syndrome, which is a lack of bilirubin glucuronidation [81, 82]. In 2004, the FDA reviewed the data on UGT1A1*28 and decided that this genetic change should be included in the insert for irinotecan as a risk factor for severe toxicity. (TA)6/(TA)6 is the normal genotype; generally, there is no change in the administered dose of irinotecan provided that no other agents known to interact with irinotecan are also administered. Patients with the (TA)6/(TA)7 heterozygous genotype have intermediate UGT1A1 activity and may be at increased risk for neutropenia; however, clinical results have been variable, and such patients have been shown to tolerate normal starting doses. Patients with the (TA)7/(TA)7 homozygous genotype should have their starting dose reduced by at least one level of irinotecan [83]. However, the precise dose reduction is not known, and subsequent dose modifications should be considered based on the individual patient's tolerance to treatment.

Recent research has shown that up to 35% of women with estrogen receptor (ER)-positive breast cancer may fail tamoxifen treatment because of drug interactions and their genetic makeup [84]. The ability of these women to convert tamoxifen to the active compound endoxifen is compromised, resulting in a greatly increased risk of relapse [85]. DNA testing and careful analysis of overall drug regimens in these patients provide evidence that can be used to improve their chances of survival. With more than 500,000 women currently taking tamoxifen, this research has wide-reaching implications.

Tamoxifen is a prodrug widely used to treat, and as prophylaxis for, ER-positive breast cancer. Out of the approximately 120,000 new ER-positive breast cancer patients per year in the IS, 41,000 of whom will die; 42,000 are predicted to fail tamoxifen treatment because of 2D6 poor metabolizer phenotype. "Hot flashes," a common side effect, are typically treated with selective serotonin reuptake inhibitors (SSRIs), many of which are potent inhibitors of CYP2D6, phenol-converting intermediate metabolizer patients into 2D6 poor metabolizers, now demonstrated as crucial to the activation of tamoxifen to endoxifen. Endoxifen has a 100 times greater receptor affinity than tamoxifen and is 30–100 times more effective. CYP2D6 genetically normal metabolizers also taking an inhibitor had 58% lower endoxifen levels and are likely to be in the group of ~35% of patients who do not respond to tamoxifen. CYP2D6 frank poor metabolizers, homozygous for *3, *4, *5, and *6, had endoxifen levels 26% of WT. CYP2D6*4/*4 poor metabolizers had a 3.12 hazard ratio for breast cancer relapse. Two-year relapse-free survival is 68% in patients with the 2D6 PM phenotype and 98% in normal metabolizers [85, 86]. This suggests that widespread genotyping and therapeutic drug monitoring could result in successful outcomes for many of the 35% of ER-positive breast cancer patients who currently fail tamoxifen treatment [87].

Dihydropyrimidine dehydrogenase (DPD) is the rate-limiting enzyme in the degradation of pyrimidine bases like thymidine and uracil [88]. DPD is also the main enzyme involved in the degradation of structurally related compounds like 5-fluorouracil (5-FU), a widely used anticancer drug [89, 90]. In 5-FU-based cancer chemotherapy, severe toxicities are observed at higher rates in patients who are heterozygous for a mutant DPYD allele, compared with toxicities in patients who are homozygous for the wild DPYD allele. The adverse effects of 5-FU are often lethal for patients homozygous for the mutant DPYD allele [91, 92].

On the basis of catalytic activity and on the basis of the mutation frequency, a 3% frequency for heterozygotes (−/+) to DPD was predicted, projecting a 1:1000 homozygote (+/+) for this mutation across racial lines.

The DPD test for 5-FU is considered appropriate for any person who is taking or considering 5-FU-based chemotherapy. It is recommended that this screening be accompanied by direct measurement of DPD activity prior to 5-FU treatment in cancer patients. Although this test looks for the most frequent genetic variation that causes DPD enzyme deficiency, this does not rule out the possibility of a decrease in DPD activity due to other factors or genetic variations [93, 94].

1.7 Summary

Drug–drug interactions with the pharmacologic results are a really important factor. More oncologists are usually aware of antineoplastic drug associations because they know the toxic side effects of each of the associated components, but they are much less aware of the pharmacologic effects of anticancer drugs and other medical treatments.

The availability of potent and reliable genetic techniques can change the way patients will receive chemotherapy in the near future. With this perspective in mind, oncologists and clinical pharmacologists should prompt the inclusion of pharmacogenetic investigation and DNA collection into early phases of clinical drug development. Recurrent, even after dose reduction, or unexplainable toxicity can be induced by genetically reduced drug inactivation/elimination. When polymorphic genes involved in the systemic disposition of a new agent are identified, prospective phenotype/genotype correlation analysis should be performed in phase I–II clinical trials, following the example of two recent phase I and pharmacogenetic studies. Pharmacogenetics has emerged as a novel and challenging area of interest in oncology.

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Breast Cancer

2

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Abstract

The appropriate selection of medical therapeutic interventions in breast cancer patients is a daily challenge for medical oncologists and takes into account disease characteristics such as stage at diagnosis, age and menopausal status, aggressiveness of the disease, and presence or absence of key therapeutic targets such as hormone receptors and HER2. Knowledge of treatment-related toxicities as well as patient's comorbidities and preferences is a critical component of an optimal estimation of the benefit versus harm ratio of a specific therapy.

This chapter reviews the side effects of the four main medical treatment modalities for breast cancer: chemotherapy, endocrine therapy, targeted agents, and bone-modifying therapeutics in terms of frequency, monitoring, and practical management.

Keywords

Breast cancer · Cytotoxic chemotherapy · Endocrine treatment · Targeted agents Bone-modifying agents · Side effects

2.1 Introduction

Appropriate selection of medical therapies for women with breast cancer requires a careful evaluation of patient and disease characteristics. The former includes age, functional status, and comorbidities, while the latter consists in stage of the disease (early versus metastatic breast cancer), presence of treatment targets such as

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M. A. Dicato, E. Van Cutsem (eds.), *Side Effects of Medical Cancer Therapy*,
https://doi.org/10.1007/978-3-319-70253-7_2

hormone receptors and HER2 overexpression or amplification, previous therapies and their effectiveness, extent and location of disease sites (visceral versus bone and soft tissue), and time course of disease.

The main objective of *adjuvant* medical treatment is to eradicate micrometastatic disease, i.e., breast cancer cells that have escaped the breast and regional lymph nodes but have not yet formed a detectable metastatic deposit.

In patients with *metastatic* disease, medical treatments are essentially palliative in nature and are directed at providing symptomatic relief from disease-related symptoms and extending progression-free survival and overall survival. Once patients have progressed through first-line therapy, their management becomes more challenging as the probability of response to subsequent therapies decreases, and this is true for sequential endocrine, anti-HER2, or chemotherapy-based approaches.

As a general rule, combination therapies have a tendency to higher efficacy in comparison to single-agent therapies, but this comes at a risk of increased toxicity.

At each stage of the disease, a careful assessment of benefit versus harm from a treatment modality is needed for each individual patient. Knowledge of treatment-induced side effects and serious toxicities is an essential component of this evaluation.

In this chapter the main side effects of cytotoxic chemotherapy, endocrine therapy, targeted agents, and bone-modifying therapeutics will be reviewed.

2.2 Chemotherapy

2.2.1 Classes of Chemotherapy and General Toxicities

2.2.1.1 Anti-microtubule Agents (Taxanes, Ixabepilone, Eribulin, and Vinca Alkaloids)

Anti-microtubule agents form a large proportion of the chemotherapy agents prescribed in breast cancer patients. These compounds either promote microtubule polymerization, stabilizing microtubules and increasing the polymer mass (anti-microtubule stabilizing agents, e.g., taxanes, ixabepilone), or inhibit microtubule polymerization, destabilizing microtubules and decreasing microtubule polymer mass (anti-microtubule destabilizing agents, e.g., eribulin, the vinca alkaloid vinorelbine) [1].

Anti-microtubule agents share the toxicities of peripheral neuropathy and myelosuppression. To note, four cycles of docetaxel can be also associated with incomplete scalp hair recovery in up to 30% of patients [2].

2.2.1.2 Anthracyclines (Doxorubicin, Epirubicin, Mitoxantrone, Liposomal Doxorubicin, and Non-pegylated Liposomal Doxorubicin)

Anthracyclines inhibit topoisomerase II, an enzyme involved in relaxing, detangling/disentangling, and cleaving of DNA and thereby inhibiting DNA transcription and replication. Further, anthracyclines can cause partial unwinding of the DNA

helix through intercalation between base pairs and can lead to the formation of free radicals, which in turn have negative effects on the cell membrane [3].

These agents share the toxicities of cardiac injury, myelosuppression, and emesis.

2.2.1.3 Antimetabolites (5-Fluorouracil, Methotrexate, Capecitabine, and Gemcitabine)

Antimetabolites have a structural similarity to precursors of pyrimidine or purines, which are the building blocks for DNA. Therefore antimetabolite agents interfere with the synthesis of DNA by not allowing these molecules to be incorporated into DNA. In addition folate and folate-derived cofactors are essential in these pathways, and antagonists to folate also provide useful cytotoxics. Three classes exist: nucleoside analogues, thymidylate synthase inhibitors, and dihydrofolate reductase inhibitors. They tend to convey the greatest toxicity to cells in the S phase [4].

These compounds have common toxicities that include mucositis, diarrhea, and myelosuppression.

2.2.1.4 Alkylating Agents (Cyclophosphamide, Cisplatin, and Carboplatin)

Alkylating agents are cell cycle nonspecific agents. They form covalent bonds with bases in DNA. This leads to cross-linkage of DNA strands or breaks in DNA as a result of repair efforts. Broken or cross-linked DNA is unable to complete normal replication or cell division. Furthermore, broken or cross-linked DNA is an activator of cell cycle checkpoints, and the cell signaling that results can precipitate apoptosis [5].

As a class, they share similar toxicities: myelosuppression, gonadal dysfunction, and rarely pulmonary fibrosis. They also hold the ability to cause "second" neoplasms, particularly leukemia.

Table 2.1 provides a detailed review of the side effects of breast cancer chemotherapy agents.

2.2.1.5 Dose-Dense Chemotherapy

Dose-dense refers to the administration of drugs with a shortened interval between treatment cycles. Human cancers, and breast cancers in particular, usually grow by non-exponential Gompertzian kinetics: in this situation, a more frequent administration of cytotoxic therapy would be a more effective way of minimizing residual tumor [6]. Administration of dose-dense chemotherapy without causing unacceptable toxicity became possible with the introduction of myeloid growth factors such as granulocyte colony-stimulating factor (G-CSF) [7].

Dose-dense anthracycline- and taxane-based chemotherapy has become a mainstay adjuvant treatment for high-risk breast cancer patients, being associated with improved survival outcomes [8]. As compared to the same regimen administered with standard interval, dose-dense chemotherapy is associated with a significant higher risk of anemia, thrombocytopenia, and mucositis [9].

Table 2.1 Side effects of chemo_2016 update

Mechanism of action	Drug	Context of prescription (NA/A/M) and usual dose schedule	Minimum requirements for prescription	SE specific to agent	Standard special tests to modify SE
Anti-microtubule: stabilizer	Paclitaxel[a]	A/M (any line) IV dose: 80–90 mg/m^2 weekly or 175 mg/m^2 D1 q 3 weekly in metastatic setting only	Nil	Hypersensitivity	Nil
				Arthralgia/myalgia	Nil
				Peripheral neuropathy (sensory)	Neurological assessments
				Bradycardia and hypotension	Monitor vital signs
Anti-microtubule: stabilizer	Docetaxel[b]	A/M (any line) IV dose: 75–100 mg/m^2 D1 q 3 weekly	Nil	Hypersensitivity	Nil
				Fluid retention	Nil
				Peripheral neuropathy (sensory)	Neurological assessments
				Alopecia	Nil
				Rash/pruritus	Nil
				Nail changes	Nil
				Hand-foot syndrome	Nil
				Teary/watery eyes	Nil
				Arthralgia/myalgia	Nil
Anti-microtubule: stabilizer	Nanoparticle, albumin-bound paclitaxel; nab-paclitaxel; protein-bound paclitaxel[e]	M.IV dose: 260 mg/m^2 D1 q 3 weekly or 100–150 mg/m^2 weekly	After failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy Prior therapy should have included an anthracycline unless clinically contraindicated	Peripheral neuropathy	Neurological assessments
				Ocular/visual disturbance	Nil
				Myelosuppression (neutropenia)	Nil

Anti-microtubule: stabilizer	Ixabepilone[g]	M.IV dose: 40 mg/m^2 D1 q 3 weekly	Monotherapy: after failure of taxane, anthracycline, and capecitabine chemotherapy Combination therapy with capecitabine: after failure of taxane and anthracycline chemotherapy	Peripheral neuropathy	Neurological assessments
				Myelosuppression (neutropenia)	Monitor blood count
				Hypersensitivity	Nil
Anti-microtubule: destabilizer	Eribulin[h]	M 3rd line and beyond IV dose: 1.4 mg/m^2 D 1,8 q 3 weekly	Prior therapy should have included an anthracycline and a taxane in either the adjuvant or metastatic setting	Myelosuppression (neutropenia)	Monitor LFTs and blood counts
				Peripheral neuropathy	Neurological assessments
				QT prolongation	ECG monitoring in patients with congestive cardiac failure bradyarrhythmias, drugs known to prolong the QT interval, including class Ia and III antiarrhythmics and electrolyte abnormalities
Anti-microtubule: destabilizer	Vinorelbine[i]	M first-line and beyond IV dose: mostly used at 20–25 mg/m^2 weekly	NA	Acute dyspnea and severe bronchospasm[j,k]	Nil
				Constipation/ileus	
				Neuropathy	Nil
				Chest pain	Nil
				Pain in tumor-containing tissue	Nil
Anthracyclines	Doxorubicin/ epirubicin[m,n]	A/M IV doses: 50–60 mg/m^2, 75–100 mg/m^2 3 weekly for doxorubicin and epirubicin respectively when used in combination	N/A	Cardiotoxicity: acute, chronic, and delayed	Cardiac assessment at baseline with clinical examination, ECG, and of LVEF assessment with radionucleotide angiography (MUGA scan) or serial echocardiogram Once cumulative dose has surpassed (see table) the threshold, regular cardiac assessment should be completed as described above and monitor for clinical symptoms of CHF prior to each cycle of anthracycline
				Hyperuricemia (rare)	Baseline and monitor EUC
				Local extravasation	Monitor infusion site for patients with difficult venous access consider central venous access device (CVAD) and contrast study

(continued)

Table 2.1 (continued)

Mechanism of action	Drug	Context of prescription (NA/A/M) and usual dose schedule	Minimum requirements for prescription	SE specific to agent	Standard special tests to modify SE
Anthracyclines	Pegylated liposomal doxorubicin[o]	M IV dose: mostly used at 40–45 mg/m^2 D1 q 4 weekly	EMA but not FDA-approved indication	Acute infusion reactions	Monitor first infusion
				Palmar-plantar erythrodysesthesia (PPE)	Monitor patient for symptoms (numbness or tingling)
				Stomatitis	Monitor patient for symptoms in each cycle
				Cardiotoxicity: acute, chronic, and delayed	Cardiac assessment at baseline with clinical examination, ECG, and of LVEF assessment with radionucleotide angiography (MUGA scan) or serial echocardiogram Once cumulative dose has surpassed (see table) the threshold, regular cardiac assessment should be completed as described above and monitor for clinical symptoms of CHF prior to each cycle of anthracycline
Anthracyclines	Non-pegylated liposomal doxorubicin[q]	M. IV dose 60–75 mg/m^2 D1 q 3 weekly	Frist line in combination with cyclophosphamide	Cardiotoxicity	Cardiac assessment at baseline with clinical examination, ECG, and of LVEF assessment MUGA or serial echocardiogram
Antimetabolite	5FU[r]/ capecitabine[s]	5FU A Dose: Mostly used as IV bolus 500–600 mg/m^2 Capecitabine M Oral dose: 2000–2500 mg/sqm divided equally between morning and evening D1–14 q 3 weeks	Capecitabine monotherapy after failure of taxanes or anthracycline or where anthracyclines are contraindicated Capecitabine combination therapy: after failure of anthracycline containing regimen	Cardiotoxicity (acute myocardial infarction, angina, dysrhythmias, cardiac arrest, cardiac failure and ECG changes)	Consider cardiac assessment for coronary ischemia in patients who are high risk (this may include cardiac stress test, coronary angiogram)
				Capecitabine: palmar-plantar erythrodysesthesia (hand-foot skin reaction)	Nil
				Hyperbilirubinemia	Monitor LFTs

Antimetabolite	Gemcitabine[t]	M first-line and beyond IV dose: 1000 mg/m^2 D1, 8 q 3 weekly	First line in combination with paclitaxel or single-agent palliative therapy	Elevated liver enzymes	Monitor LFTs
				Hemolytic uremic syndrome (HUS)	Monitor renal function and blood count
				Pulmonary toxicity acute dyspnea and severe pulmonary toxicities (pulmonary edema, interstitial pneumonitis and adult respiratory distress syndrome)	Nil
				Fever/flu-like symptoms	Nil
				Skin rash	Nil
				Vascular toxicity (thrombotic microangiopathy, veno-occlusive disease, and digital ischemic changes and necrosis)	Nil
Antimetabolite	Methotrexate[u]	A/M IV dose: 40 mg/m^2 D1,8 q 4 weekly	Nil	Hepatotoxicity	Monitor LFTs
				Pulmonary toxicity: acute, subacute, or chronic (inflammation, pulmonary infections, and pulmonary lymphoma[w])	Nil
				Neurological toxicity (intrathecal (IT) and high-dose methotrexate)	Nil
Alkylating agents	Cyclophos-phamide[x]	A/M IV dose 500–600 mg/sqm D1 q 3 weekly Oral dose: 100 mg/sqm daily D1–14 q 4 weeks or 50 mg continuous daily dose	Nil	Cardiac toxicity (ECG changes, elevation of cardiac enzymes, myocarditis, and myocardial necrosis)	Baseline ECG
				Hemorrhagic cystitis	Nil

(continued)

Table 2.1 (continued)

Mechanism of action	Drug	Context of prescription (NA/A/M) and usual dose schedule	Minimum requirements for prescription	SE specific to agent	Standard special tests to modify SE
Alkylating agents	Cyclophosphamide	Adjuvant or metastatic		Immunogenicity: reduced skin test antigens (e.g., tuberculin purified protein derivative)	Nil
			Nil	Interstitial fibrosis	Nil
				Nasal stuffiness or facial discomfort	Nil
				Radiation recall reaction	Nil
				SIADH	Nil
				Secondary malignancies	Nil
				Fluid retention and dilutional hyponatremia	Nil
Alkylating agents	Carboplatin[z]	A/M IV dose: AUC 6	Adjuvant HER2+ patients or metastatic	Myelosuppression (most commonly thrombocytopenia, but leukopenia, neutropenia, and anemia can also occur)	Monitor blood count
				Hypersensitivity	
				Nephrotoxicity	Monitor renal function

Mechanism of action	Risk factors and recommendation for prevention of SE	Recommendation for management of SE	In the elderly (≥65 years)	Metabolism	Excretion	Cross BBB
Anti-microtubule: stabilizer	Premedication with corticosteroids with or without antihistamines (H1 and H2 antagonists)	Stop infusion Supportive therapy with oxygen and hydration if hypotension Administer IV corticosteroids and antihistamines Infusion can be recommenced at slower rate if symptoms are mild and complete recovery has occurred Treat anaphylaxis if it occurs Prophylaxis prior to next infusion with premedication: IV corticosteroids and antihistamines Slow infusion Patients should not be rechallenged if anaphylaxis has occurred	Reduced clearance	Hepatic cytochrome P450 enzymes primarily CYP2C8/9 and CYP3A4	Biliary	No
	Nil	Symptomatic treatment with paracetamol, NSAIDS, gabapentin, and prednisone (if severe cases) In the curative setting, dose reduction is not recommended				
	Previous neurotoxic chemotherapy frequency and severity related to cumulative doses	Mostly sensory neuropathy. Toxicity may be dose limiting. Sensory manifestations usually resolve after several months of discontinuation Grade 2 neuropathy: reduce paclitaxel by 25% Grade 3 and 4: omit paclitaxel				
	Nil	These are usually minor and occur during administration and do not require treatment Rare severe cardiac conduction abnormalities have been reported, and appropriate therapy should be administered with continuous cardiac monitoring				

(continued)

Table 2.1 (continued)

Mechanism of action	Risk factors and recommendation for prevention of SE	Recommendation for management of SE	In the elderly (≥65 years)	Metabolism	Excretion	Cross BBB
Anti-microtubule: stabilizer	Premedication with corticosteroids with or without antihistamines (H1 and H2 antagonists)	Stop infusion Supportive therapy with oxygen and hydration if hypotension Administer IV corticosteroids and antihistamines Infusion can be recommenced at slower rate of infusion if symptoms are mild and complete recovery has occurred Treat anaphylaxis if it occurs Prophylaxis prior to next infusion with premedication: IV corticosteroids and antihistamines. Slow infusion Sodium cromoglycate has been used in prophylaxis in severe reactions Patients should not be rechallenged if anaphylaxis has occurred	Nil	CYP3A	Primarily biliary/fecal	Low levels found in animal studies
	Premedication with dexamethasone or methylprednisolone[c]	Slowly reversible if treatment is discontinued; however, early aggressive diuretic may be required or aspiration of fluid in pleural space for symptomatic treatment				
	Nil	Usually cumulative doses >600 mg/m^2 Grade 2 neuropathy Reduce docetaxel by 25% Grade 3 and 4: omit docetaxel				
	Nil	Self-limiting. Poor hair regrowth or persistent hair loss occasionally reported				
	Avoid perfumed skin products	Self-limiting Antihistamines for pruritus				
	Some benefit from application of dark nail varnish	Cold-induced vasoconstriction by wearing frozen gloves during treatment may reduce nail toxicity Cosmetic changes disappear once treatment is withdrawn Nail bed infections are treated with topical antibiotics or antifungals if necessary				
	Nil	May respond to administration of pyridoxine				
	Nil	Associated with cumulative dosing and occurs after a median of 400 mg/m^2 treatment with artificial tears or other ocular moisturizers may ameliorate symptoms In the case of severe symptoms, lacrimal duct obstruction must be ruled out[d]				
	Nil	Symptomatic treatment with paracetamol, NSAIDS, gabapentin, and prednisone (if severe cases) In the curative setting, dose reduction is not recommended				

Anti-microtubule: stabilizer	Influenced by prior and/or concomitant therapy with neurotoxic agents Dose-dependent	Grade 3 drug interruption until resolution followed by dose reduction for subsequent cycles severe symptoms of sensory neuropathy improve with a median of 22 days after treatment interruption[f]	Improved compared to paclitaxel	Liver (primarily via CYP2C8, minor CYP 34A)	Extensive non renal	No information available
	Higher than recommended doses	Most commonly reversible keratitis and blurred vision Rare persistent optic nerve damage reported				
	Administration of granulocyte colony-stimulating factor (G-CSF) Do not give therapy if neutrophil count $<1.5 \times 10^9$/L	Usually rapidly reversible Antimicrobials should be commenced for evidence of fever, and patients with febrile neutropenia should be treated with appropriate antibiotics Dose reductions for neutropenia lasting >1 week for subsequent cycles				
Anti-microtubule: stabilizer	Patients with diabetes mellitus or preexisting peripheral neuropathy may be at increased risk of severe neuropathy. Prior therapy with neurotoxic chemotherapy agents did not predict the development of neuropathy	Sensory manifestations usually resolve to baseline or grade 1, within twelve weeks upon treatment discontinuation	no effects, but limited experience in clinical trials	Liver via CYP3A4	Faces	No information available
	Do not give therapy if neutrophil count $<1.5 \times 10^9$/L	Delay administration of and reduce subsequent doses in patients who experience severe neutropenia or thrombocytopenia				
	Risk factor hypersensitivity reactions to polyoxyethylated castor oil or its derivatives Premedication with IV corticosteroids and antihistamines (H1 and H2 antagonists)	Stop infusion Supportive therapy with oxygen and hydration if hypotension Administer IV corticosteroids and antihistamines Infusion can be recommenced at slower rate if symptoms are mild and complete recovery has occurredTreat anaphylaxis if it occurs Prophylaxis prior to next infusion with premedication: IV corticosteroids and antihistamines Slow infusion Patients should not be rechallenged if anaphylaxis has occurred				

(continued)

Table 2.1 (continued)

Mechanism of action	Risk factors and recommendation for prevention of SE	Recommendation for management of SE	In the elderly (≥65 years)	Metabolism	Excretion	Cross BBB
Anti-microtubule: destabilizer	Elevated liver transaminases (>3× ULN) and bilirubin >1.5 × ULN Do not give therapy if neutrophil count $<1.5 \times 10^9$/L	Delay administration of and reduce subsequent doses in patients who experience febrile neutropenia or grade 4 neutropenia lasting longer than 7 days	No effects, but limited experience in clinical trials	Feces	Feces	No information found
	Nil	Withhold in patients who experience grade 3 or 4 peripheral neuropathy until resolution to grade 2 or less				
	Avoid in high-risk patients	Correct hypokalemia or hypomagnesemia prior to initiating therapy, and monitor these electrolytes periodically during therapy Avoid in patients with congenital long QT syndrome				
Anti-microtubule: destabilizer	Risk factors include concurrent mitomycin	May respond to bronchodilators' subacute pulmonary reactions characterized by cough, dyspnea, hypoxemia, and interstitial infiltration; may respond to corticosteroid therapy and oxygen; may provide symptomatic relief		Hepatic cytochrome P450 enzymes	Biliary	Brain and plasma levels are comparable in animal studies[1]
	Prior treatment with other neurotoxic chemotherapy may result in cumulative toxicity	Mild to moderate peripheral neuropathy is usually reversible upon discontinuation Also can cause severe constipation (G3-4), paralytic ileus, intestinal obstruction, necrosis, and/or perforation				
	Nil	Cardiovascular disease or tumor within the chest is a risk factor				
	Nil	Acute pain syndrome within 30 min of infusion can occur at the tumor site after the first dose. Usually lasts from 1 h to several days. Management is with corticosteroids and narcotic analgesia if necessary				

Anthra-cyclines	Cumulative doses must be calculated, and monitoring is as per cumulative dose (see table)	A reduction in LVEF of 10% to below the lower limit of normal, 20% reduction at any level, or an absolute LVEF ≤45% indicates deterioration in cardiac function The gold standard for diagnosis of anthracycline-induced cardiotoxicity is endomyocardial biopsy. However rarely performed due to its invasive nature Management of congestive cardiac failure. This can include low-salt diet, diuretics, ACE inhibitors or angiotensin receptor blockers, inotropes, and cardiac transplantation	Doxorubicin: no information Epirubicin: clearance may be decreased	Doxorubicin: in the liver and other tissue by an aldo-keto reductase enzyme Epirubicin: Extensive hepatic metabolism also metabolized by other organs including RBC	Doxorubicin: predominately Bile Predominately hepatobiliary; rapid elimination of parent compound from plasma	No
	Prophylactic treatment for high-risk patients includes aggressive hydration, discontinuation of drugs that cause hyperuricemia (e.g., thiazide diuretics) or acidic urine (e.g., salicylates), monitor electrolytes and replace as required, and alkalinize the urine, allopurinol/rasburicase orally Note: allopurinol can be given IV for patients not tolerating oral medications	Treatment of tumor lysis syndrome includes maintaining aggressive hydration with target urine output >100 mL/h, maintenance of urine pH at 7.0 with administration of sodium bicarbonate allopurinol or rasburicase monitoring, replacement and maintenance of serum electrolytes (calcium, phosphate, renal function, LDH and uric acid). Hemodialysis if necessary				
	Ensure adequate peripheral access Administration time 15–20 mins Monitor for erythematous streaking along the vein and/or facial flushing	Management of extravasation: stop the injection/infusion, and disconnect the intravenous tubing Withdraw as much of the drug as possible, via existing cannula or CVAD. Mark area of the skin with indelible pen. Take a photograph of the area as soon as possible Elevate and apply compression to the limb If appropriate, remove the peripheral cannula (do not remove the CVAD) Utilize extravasation kit Apply Cold pack Apply 98–99% dimethyl sulfoxide (DMSO) topically to the skin within 10–25 min following local protocols Urgent assessment by plastic surgeon				

(continued)

Table 2.1 (continued)

Mechanism of action	Risk factors and recommendation for prevention of SE	Recommendation for management of SE	In the elderly (≥65 years)	Metabolism	Excretion	Cross BBB
Anthracyclines	Administer initial dose no faster than 1 mg/min	Slow or interrupt the rate of infusion antihistamines H2 blockers steroids	No pharmacokinetics effect on drug	As per doxorubicin	As per doxorubicin but significantly slower allowing for approximately two to three orders of magnitude larger AUC than for a similar dose of conventional doxorubicin	No
	If symptoms are present, consider increasing the dosing interval Pyridoxine (50–150 mg/day) may be used for prophylaxis without affecting the antitumor activity Prophylactic corticosteroids may be of benefit[p] Avoidance of skin stressors/ pressure measures to decrease PPE following infusion (e.g., avoidance of tape on skin, sun exposure, hot water, pressure, or friction on the skin)	Mild reactions resolve independently within 1–2 weeks More severe reactions may require a discontinuation of therapy and corticosteroid use may assist in resolution				
	Generally associated with higher doses, prior alcohol and tobacco use, poor nutritional status and dental hygiene, and concomitant use of antihistamines, anticholinergics, phenytoin, and steroids	Dose modification as per guidelines of institution				
	Occurs at lower frequency than conventional doxorubicin Care should be exercised in patients who have received prior anthracycline therapy or in those patients that have a history of cardiovascular disease. LVEF assessments should be performed more frequently in this patient population Cumulative doses must be calculated, and monitoring is as per cumulative dose (see table)	Treatment for congestive heart failure is as per doxorubicin/ epirubicin				

Anthracyclines	Occurs at lower frequency than conventional doxorubicin Care should be exercised in patients who have received prior anthracycline therapy or in those patients that have a history of cardiovascular disease. LVEF assessments should be performed more frequently in this patient population Cumulative doses must be calculated, and monitoring is as per cumulative dose (see table)	Treatment for congestive heart failure is as per doxorubicin/epirubicin	Cardiac safety comparable in patients <65 years and >65 years	Hepatobiliary	Hepatobiliary	No information available
Antimetabolite	Patient screening	Risk factors include prior history of coronary artery diseases Management includes discontinuation of 5FU/capecitabine	No clinically significant difference in PK, but side effects need to be carefully monitored in this population due to impaired renal function which should lead to a dose reduction of capecitabine	Hepatic	Renal	Limited evidence in HER2 +BC in combination with anti-HER agents
	Behavioral modifications: avoid tight fitting shoes or repetitive rubbing pressure to hands and feet apply lanolin-containing creams to affected areas	Behavioral modifications reactions ≥ grade 2 severity (skin changes with pain but not interfering with function); therapy should be interrupted and recommenced at a reduced dose when symptoms resolve to grade 1				
	Nil	If hyperbilirubinemia ≥grade 2 (serum bilirubin >1.5 times the upper limit of normal), therapy should be interrupted until hyperbilirubinemia resolves and subsequent dose reductions may be needed for subsequent dosing				

(continued)

Table 2.1 (continued)

Mechanism of action	Risk factors and recommendation for prevention of SE	Recommendation for management of SE	In the elderly (≥65 years)	Metabolism	Excretion	Cross BBB
Antimetabolite	Nil	Usually transient and reversible elevations of liver function enzymes in about two thirds of patients increases are rarely of clinical significance, and there is no evidence of hepatic toxicity with longer duration or cumulative doses	Decreased clearance and increased half-life with increasing age	Intracellularly by nucleoside kinases	Renal	No information available
	Nil	Onset during and shortly after gemcitabine therapy (4–8 weeks post completion of therapy up to several months); monitor renal function closely especially in patients with impaired renal function; therapies can include immunocomplex removal (plasmapheresis, immunoadsorption, or exchange transfusion), antiplatelet/anticoagulant therapies, immunosuppressive therapies, and plasma exchange Rituximab has been successfully used in patients with chemotherapy-induced HUS Case fatality rate is high				
	Risk factors include prior irradiation to the mediastinum. Use caution when prescribing in this patient population	Acute dyspnea is usually self-limiting, symptomatic relief with oxygen Severe pulmonary toxicities usually occur after several cycles but can occur after a single cycle Discontinuation of drug and early supportive care with bronchodilators, corticosteroids, diuretics, and/or oxygen pulmonary toxicities may be reversible, but fatal recurrences have been reported in patients rechallenged				
	Nil	Symptoms are mild to transient and rarely dose-limiting acetaminophen may provide relief				
	Nil	Not dose limiting responds to topical corticosteroids and antihistamines				
	Suggested to be more common after cumulative doses of 10,000 mg/m^2 or in the setting of combination therapy	Treat as per type of vascular toxicity				

Antimetabolite	Avoid alcohol, medications, or herbal supplements that may increase the risk of hepatotoxicity	Liver enzymes may increase with each cycle and return to pretreatment levels after discontinuation for 1 month Note: cirrhosis usually occurs with chronic low dose, and if it occurs, it should be managed as per guidelines for cirrhosis management		Hepatic and intracellular	Renal	Ratio of 10–30: 1 for CNS concentration[v]
	Nil	Subacute toxicity includes dyspnea, nonproductive cough, fever, crackles, cyanosis, pulmonary fibrosis, and pleural effusions. Treatment includes discontinuation of methotrexate and corticosteroid therapy. Rechallenge is not recommended Pulmonary infections with opportunistic pathogens should be treated for individual pathogen Pulmonary lymphoma regresses after discontinuation of methotrexate. Rechallenge is not recommended				
	Intrathecal methotrexate: aseptic meningitis, IT hydrocortisone, or oral corticosteroids Transverse myelopathy: risk factors include frequent IT methotrexate, concurrent radiotherapy Leukoencephalopathy: risk factors include whole brain radiotherapy and IV methotrexate	IT methotrexate: aseptic meningitis (onset hrs): no treatment required Patients can be rechallenged Transverse myelopathy (onset hrs-days): no specific intervention, recovery variable and patients should not be rechallenged Leukoencephalopathy (onset delayed): there is no uniform therapeutic approach. Available therapies include corticosteroids and leucovorin Note: other neurological sequelae include encephalopathy, seizures, neurological deficits, lumbosacral radiculopathy, neurogenic pulmonary edema, and sudden death High-dose methotrexate: acute neurotoxicity (onset within 24hrs): usually spontaneous resolution. Rechallenge is possible Subacute neurotoxicity - stroke-like syndrome (onset approx. 6 days after administration): resolves in minutes to days. Rechallenge is possible Leukoencephalopathy: as above				

(continued)

Table 2.1 (continued)

Mechanism of action	Risk factors and recommendation for prevention of SE	Recommendation for management of SE	In the elderly (≥65 years)	Metabolism	Excretion	Cross BBB
Alkylating agents	Risk factors include chest or mediastinal radiotherapy and anthracycline administration Effect is not attributable to cumulative dosing Occurs in high dose (60 mg/kg daily or 120–270 mg/kg over a few days)	Supportive treatment	No clinically significant difference in PK	Hepatic cytochrome P450 enzymes primarily CYP2B6[y]	Enzymatic oxidation to active and inactive metabolites excreted in urine	Penetration
	Risk factors include long-term use, high dose, rate of infusion, poor hydration status, decreased urine output, concurrent exposure to other urotoxic drugs, or genitourinary radiotherapy; encourage oral intake of fluids in 24–48 h prior to therapy and during therapy. Drug administration should be completed early in the day to avoid the drug sitting in the bladder overnight Other measures include administration of mesna (rarely needed for doses <2 g/m^2), catheter bladder drainage, bladder irrigation, intravenous hydration with diuresis, hyperhydration (not routinely recommended)	Discontinuation of cyclophosphamide, increase fluid intake, maintain platelet count at >50,000/mm^3 Cystitis: first-line therapy; hyperhydration Second-line therapy: bladder irrigation Third-line therapy: prostaglandin into the bladder Late onset cystitis (usually due to secondary viral or bacterial infection): culture for bacterial pathogens, cytomegalovirus (CMV), and adenovirus; hyperhydration ± bladder irrigation; treat pathogen if isolated				

Alkylating agents	Nil	Nil	No clinically significant difference in PK	Hepatic cytochrome P450 enzymes primarily CYP2B6	Enzymatic oxidation to active and inactive metabolites excreted in urine	Penetration
	Risk factors include long-term exposure, exposure to other drugs with pulmonary toxicities, and pulmonary radiotherapy	Condition may be non-reversible and fatal Discontinuation of drug and initiation of corticosteroids Exclude other causes of pulmonary toxicity such as opportunistic infections				
	Associated with rapid injection Slow the infusion rate Intermittent infusion rather than IV bolus	Analgesics, decongestants, antihistamines, intranasal steroids, or ipratropium				
	Nil	Usually resolves after several days Treatment may include topical steroids or nonsteroidal anti-inflammatories for radiation recall dermatitis				
	More common with doses of >50 mg/kg and aggravated by large volumes of hydration given to prevent hemorrhagic cystitis	Self-limiting Diuretic therapy may be useful when the patient has stopped voiding				
	Nil	Treatment for individual malignancy				
	Associated with doses >30–40 mg/kg	Self-limiting within 24 h of therapy				
Alkylating agents	Risk factors include prior chemotherapy, poor performance status, increasing age, impaired renal function and concurrent myelosuppressive therapy Dose dependent and can be minimized by using the Calvert AUC-based dose formula	Anemia may be corrected with transfusions dose as per Calvert AUC-based dose formula	Clearance may be reduced due to age-related renal function impairment	Intracellular	Renal	Yes
	Risk associated with repeated exposure to platinum agents especially with a second course of platinum therapy	Treat anaphylaxis if it occurs Carboplatin therapy can be continued in some cases with prophylactic corticosteroid and antihistamine and/or desensitization				
	Dose as per Calvert AUC-based dose formula	Nil				

(continued)

Table 2.1 (continued)

[a]Squibb BM: Taxol® product monograph

[b]Sanofi: Docetaxel product monograph

[c]Piccart MJ, Klijn J, Paridaens R, Nooij M, Mauriac L, Coleman R, Bontenbal M, Awada A, Selleslags J, Van Vreckem A, Van Glabbeke M: Corticosteroids significantly delay the onset of docetaxel-induced fluid retention: Final results of a randomized study of the european organization for research and treatment of cancer investigational drug branch for breast cancer. J Clin Oncol 1997;15:3149-3155

[d]Esmaeli B, Hidaji L, Adinin RB, Faustina M, Coats C, Arbuckle R, Rivera E, Valero V, Tu SM, Ahmadi MA: Blockage of the lacrimal drainage apparatus as a side effect of docetaxel therapy. Cancer 2003;98:504-507

[e]Celgene: Abraxane product monograph

[f]Gradishar WJ, Tjulandin S, Davidson N, Shaw H, Desai N, Bhar P, Hawkins M, O'Shaughnessy J: Phase iii trial of nanoparticle albumin-bound paclitaxel compared with polyethylated castor oil-based paclitaxel in women with breast cancer. J Clin Oncol 2005;23:7794-7803

[g]Squibb BM: Ixempra® product monograph

[h]Eisai: eribulin product monograph

[i]Pharmaceuticals PF: Navelbine® product monograph

[j]Rouzaud P, Estivals M, Pujazon MC, Carles P, Lauque D: [respiratory complications of the vinorelbine-mitomycin combination]. Rev Mal Respir 1999;16:81-84

[k]oli AK, Osman MN, Koduri M, Byrd RP, Roy TM: A case report of vinorelbine monotherapy-related acute bronchospasm and non-st elevation acute coronary syndrome. Tenn Med;104:47-48

[l]Gregory RK, Smith IE: Vinorelbine--a clinical review. Br J Cancer 2000;82:1907-1913

[n]Medicines TP: Doxorubicin product monograph

[m]Medicines TP: Epirubicin product monograph

[o]Janssen: Caelyx® product monograph

[p]Alberts DS, Muggia FM, Carmichael J, Winer EP, Jahanzeb M, Venook AP, Skubitz KM, Rivera E, Sparano JA, DiBella NJ, Stewart SJ, Kavanagh JJ, Gabizon AA: Efficacy and safety of liposomal anthracyclines in phase i/ii clinical trials. Semin Oncol 2004;31:53-90

[q]Agencies EM: Myocet® summary of product characteristics

[r]Information OF: 5-fluorouracil product information

[s]Genentech: Xeloda® product monograph

[t]Lilly: Gemzar® product monograph

[u]Pfizer: Methotrexate product monograph

[v]Qin D, Ma J, Xiao J, Tang Z: Effect of brain irradiation on blood-csf barrier permeability of chemotherapeutic agents. Am J Clin Oncol 1997;20:263-265

[w]Ebeo CT, Girish MR, Byrd RP, Roy TM, Mehta JB: Methotrexate-induced pulmonary lymphoma. Chest 2003;123:2150-2153

[x]Squibb BM: Cytoxan®

[y]Chang TK, Weber GF, Crespi CL, Waxman DJ: Differential activation of cyclophosphamide and ifosphamide by cytochromes p-450 2b and 3a in human liver microsomes. Cancer Res 1993;53:5629-5637

[z]Information OF: Carboplatin product information

2.2.2 Incidence and Management of Selected Chemotherapy Toxicities

This section outlines some of the common toxicities associated with breast cancer chemotherapy and their management. Many of the frequent toxicities induced by cytotoxic drugs commonly prescribed to breast cancer patients such as myelosuppression and gastrointestinal toxicity are reviewed in other chapters of this book. Only a few toxicities are discussed in detail below.

2.2.2.1 Febrile Neutropenia

Febrile neutropenia is a life-threatening condition of a number of chemotherapy regimens, and its proper prevention and/or management is described in Chap. 16 of this book.

As far as breast cancer chemotherapy is concerned, particular attention needs to be paid to patients receiving docetaxel: the rate of febrile neutropenia with docetaxel at 100 mg/m^2 is 15–25% [10, 11]. In this scenario, prophylactic G-CSF is highly recommended.

Anthracycline-based regimens are associated with an intermediate risk (10–20%) of febrile neutropenia [12]. The addition of 5-fluorouracil to anthracycline and cyclophosphamide proved to be associated with no survival benefit but higher toxicity (including myelotoxicity) [13].

Febrile neutropenia is less common with other "popular" breast cancer chemotherapy regimens such as "CMF" (cyclophosphamide, methotrexate, 5-fluorouracil), weekly paclitaxel, vinorelbine, or capecitabine.

2.2.2.2 Management of Chemotherapy-Induced Emesis

Management of chemotherapy-induced nausea and vomiting is an essential component in the care of all patients receiving breast cancer chemotherapy and is described in Chap. 18.

Chemotherapy regimens used in breast cancer have different potentials to induce emesis (see Table 2.2) [14, 15].

Table 2.2 Emetogenic potential of breast cancer chemotherapy agents [14, 15]

Level	Agents in breast cancer
High emetic risk (>90% frequency of emesis without prophylaxis)	Combination doxorubicin/epirubicin with cyclophosphamide Cyclophosphamide IV >1500 mg/m^2 Doxorubicin >60 mg/m^2 Epirubicin >90 mg/m^2
Moderate emetic risk (30–90% frequency of emesis)	Carboplatin Cyclophosphamide IV ≤1500 mg/m^2 Cyclophosphamide oral (≥100 mg/m^2/day) Doxorubicin ≤60 mg/m^2 Epirubicin ≤90 mg/m^2 Methotrexates IV ≥250 mg/m^2
Low emetic risk (10–30% frequency of emesis)	Docetaxel Liposomal doxorubicin 5-Fluorouracil Gemcitabine Methotrexate >50 mg/m^2 and <250 mg/m^2 Paclitaxel Paclitaxel albumin Cyclophosphamide oral (<100 mg/m^2/day) Methotrexate oral Capecitabine Eribulin Ixabepilone
Minimal emetic risk (<10% frequency of emesis)	Methotrexate <50 mg/m^2 Vinorelbine

Again, the addition of 5-fluorouracil to anthracycline and cyclophosphamide is associated with higher toxicity including grade ≥3 nausea and vomiting and no survival benefit [13].

2.2.2.3 Peripheral Neuropathy

Several classes of cytotoxic agents can induce chemotherapy-induced peripheral neuropathy (CIPN) (see Table 2.1 for a detailed review of agents inducing neuropathy). Taxanes, ixabepilone, vinorelbine, eribulin, and platinum compounds are the most likely cause of neuropathy in breast cancer patients.

The development of CIPN is one of the most common reasons for discontinuation of chemotherapy, and its occurrence can affect the long-term quality of life of patients. Although neuropathy is a common complication and is associated with necessary dose reductions, its development does not seem to be associated with a higher risk of recurrence or inferior survival [16].

Comorbidities, such as diabetes and alcohol abuse, predispose patients to toxic nerve fiber damage from chemotherapy [17]. Common symptoms include burning sensation, tingling, loss of feeling, walking difficulties, trouble using fingers, poor balance, sensitivity to temperatures, loss of reflexes, and constipation. Prevention of severe CIPN is the cornerstone of management. This requires regular neurological assessment of patients prior to each scheduled chemotherapy administration. CIPN usually resolves gradually over time, but it may be irreversible.

According to the American Society of Clinical Oncology (ASCO) guidelines, there are no agents recommended for the prevention of CIPN [18]. For the treatment of existing CIPN, a moderate recommendation has been given for treatment with duloxetine [18]. Trials evaluating tricyclic antidepressants (e.g., nortriptyline or desipramine), gabapentin, and a compounded topical gel (containing baclofen, amitriptyline HCL, and ketamine) were inconclusive; however, these agents may be offered on the basis of data supporting their utility in other neuropathic pain conditions [18].

It is possible that pharmacogenetic studies will reveal particular genotypes at greater risk for CIPN [19].

2.2.2.4 Cardiac Failure

Anthracyclines are highly effective drugs in breast cancer but have the significant drawback of inducing cardiac failure. Acute, chronic, and delayed cardiotoxicity has been described. Acute cardiotoxicity is not dose-related, may occur immediately after a single dose of anthracycline, and usually involves ECG changes such as arrhythmias, T-wave flattening, ST depression, and prolongation of QT interval [20]. It is usually transient and does not require treatment intervention [20]. Rarely pericarditis, myocarditis, or cardiac failure occurs [20]. Chronic cardiac toxicity, in the form of irreversible cardiomyopathy, is dose-related and indolent in onset [20]. It generally presents within 1 year of treatment with signs and symptoms of reduced left ventricular ejection fraction [20]. Delayed cardiotoxicity occurring many years after exposure to anthracycline is also described and thought to be dose-related and irreversible [20]. The mechanism of chronic and

delayed anthracycline-related cardiotoxicity seems to be related to the generation of free radicals with consequent oxidative stress and death of cardiomyocytes [21].

The risk of cardiotoxicity from anthracycline is dose-related [21]. In a retrospective analysis of phase III trials (n = 613), the estimated cumulative percentages of patients developing doxorubicin-related congestive heart failure were 5% at a cumulative dose of 400 mg/m^2, 26% at a dose of 550 mg/m^2, and 48% at a dose of 700 mg/m^2 [22].

Due to the risk of cardiomyopathy, a lifetime maximum dose places limits on continued anthracycline administration (see Table 2.1) [23]. In addition to the cumulative dose, several patient characteristics (i.e., preexisting heart disease, hypertension, diabetes, previous anthracycline exposure at an early age, previous mediastinal radiotherapy, old age) can predispose to the development of this side effect [21]. Co-administration with anti-HER2 agents is associated with increased risk of cardiotoxicity and is discussed further in this chapter [24]. In all these situations, cardiotoxicity may occur at lower doses.

Table 2.1 describes the management of anthracycline-induced cardiac failure.

Several approaches to reduce the cardiotoxicity of anthracyclines have been investigated. Dexrazoxane is a chelating agent that acts by binding iron intracellularly, thus preventing hydroxyl radical formation in the presence of anthracyclines [25]. Hence, this compound may prevent cardiac injury. Unfortunately, a phase III trial evaluating this agent in 682 patients with advanced breast cancer therapy revealed a significant cardioprotective effect of dexrazoxane but a lower objective response rate (46.8 vs 60.5%; 95% Cl, −25 to −2%; P = 0.019) [26]. The ASCO guidelines do not recommend routine use of dexrazoxane in either the adjuvant or metastatic settings with initial doxorubicin-based chemotherapy, but it may be considered in metastatic breast cancer patients who have received more than 300 mg/m^2 of doxorubicin and are thought to benefit from continued doxorubicin-containing therapy [27].

The second approach involves altering the schedule of anthracyclines. A retrospective study revealed significant reduction in the probability of clinically overt cardiomyopathy occurring at a cumulative dose of 550 mg/m^2 when doxorubicin was given weekly as opposed to every 3 weeks' schedule [28].

A third approach consists in prolonging the anthracycline infusion time: nonrandomized data from MD Anderson Cancer Center suggest a cardioprotective effect in delivering anthracyclines as a 96 h infusion versus bolus doses [29].

Two novel anthracyclines deserve specific mention due to their reduced cardiac toxicity profile: pegylated liposomal doxorubicin and non-pegylated liposomal doxorubicin. Studies in the first-line setting showed better cardiac toxicity profile with similar antitumor effects for both agents [30, 31]. A Bayesian network meta-analysis showed that liposomal doxorubicin is less cardiotoxic than doxorubicin (odds ratio [OR] 0.60; 95% CI, 0.34–1.07), but there was no difference in cardiotoxicity as compared to epirubicin (OR 0.95; 95% CI, 0.39–2.33) [32]. Doxorubicin showed to be more cardiotoxic than non-anthracycline-based regimens (OR 1.57; 95% CI, 0.90–2.72) [32].

2.2.2.5 Gastrointestinal Side Effects: Mucositis, Diarrhea, and Constipation

Diarrhea is a side effect of certain chemotherapy agents such as 5-fluorouracil and capecitabine. Diarrhea is associated with fluid and electrolyte loss as well as a decrease of the quality of life. Grade 3 or 4 toxicity may require dose reductions (which may affect the efficacy of the chemotherapy regimens). Other causes of diarrhea such as infections should always be excluded.

Assessment should include a complete blood count, blood chemistry, and stool analyses for bacterial, fungal, and parasites or viral pathogens. Abdominal imaging may be indicated as well as occasionally endoscopy to rule out confounding causes of diarrhea.

Treatment guidelines for patients with chemotherapy-induced diarrhea have been published [33]. The basis of management is fluid rehydration and electrolyte replacement, and antibiotics should be used for persistent diarrhea and/or for long-term neutropenic patients. Dietary modifications such as avoidance of lactose, caffeinated beverages, and alcohol should be encouraged [34]. Pharmacological therapies for chemotherapy-induced diarrhea involve agents such as loperamide [35]. Other agents that show benefit include opioids and octreotide [36]. Grade 3 or 4 toxicity may also require chemotherapy dose reductions (see Table 2.1 for detailed management for individual chemotherapy agents).

Chemotherapy-induced mucositis can be a dose-limiting toxicity in treatment with anthracyclines, 5-fluorouracil, capecitabine, and methotrexate. Combination therapy, previous episodes of mucositis with previous treatment cycles, and several patient-related risk factors (e.g., comorbidities such as malnutrition) may increase the risk and severity of oral mucositis [37].

Preventive measures are important in reducing the risk of developing and the severity of mucositis: sources of trauma (e.g., sharp edges and ill-fitting prostheses) should be eliminated, and painful stimuli (e.g., hot foods and drinks and hard, sharp, or spicy foods) should be avoided [37]. Effective oral hygiene is crucial [37].

For the prevention or treatment of oral mucositis, the available evidence does not support dental care, normal saline, sodium bicarbonate, mixed medication mouthwash, and chlorhexidine in patients receiving chemotherapy [38]. Hence, no recommendation in favor of normal saline mouthwashes is possible; on the contrary, plain water can be used [37].

Treatment is mostly supportive with good oral hygiene, mouthwashes, and analgesia [39]. Small trials with agents such as glutamine [40], AES-14 [41], and various growth factors [42–44] have been explored with inconclusive results. Athermic laser is effective in the prevention and management of mucositis [45]. Doxepin mouthwash (0.5%) may be effective to treat pain due to oral mucositis [37].

Constipation is often associated with concomitant medication use such as 5-HT3 antagonists, antidiarrheal agents, or opioid therapy. Sinister causes for constipation such as spinal cord compression or bowel obstruction due to malignancy should be excluded with imaging.

Behavioral modifications such as increased dietary fiber, exercise, and increased fluid intake should be encouraged. Pharmacotherapy with stool softeners may also be utilized.

2.2.2.6 Cognitive Dysfunction

Neurotoxicity of chemotherapy agents also extends to cognitive function. Various terms have been used to describe this phenomenon: "chemo brain" or "chemo fog" [46]. Patients often describe a vagueness and difficulty in planning. However, to date, the role of chemotherapy neurotoxicity in the causation of cognitive dysfunction is still unclear.

A growing recognition of this occurrence has in turn resulted in extensive literature. A meta-analysis of six studies revealed that women who received adjuvant chemotherapy for breast cancer were affected by cognitive impairments [47]. Most studies tend to report a mixed diffuse cognitive pattern on neuropsychological testing with the most compromising functions being verbal learning and memory as well as attention and concentration which are in line with front striatal dysfunction [48–50]. This has been seen in breast cancer patients, and a dose-dependent effect with more cycles of chemotherapy linked to lower neuropsychological scores has been described [51]. Although high rates (>60% of patients) have been sporadically reported [52], only a minority (15–25%) of treated women seemed to be affected [53].

Cognitive dysfunction can persist for years after the completion of chemotherapy, and 5-fluorouracil has been implicated as a potential agent [54, 55]. However, a meta-analysis including 17 neuropsychological studies showed that at least 6 months after the end of standard chemotherapy regimen for breast cancer, cognitive deficits seemed to be, on average, small in magnitude and limited to the domains of verbal ability and visuospatial ability [56].

Patients and carriers need to be educated about its occurrence. As recommended by the ASCO guidelines, primary care clinicians should ask patients if they are experiencing cognitive difficulties and should assess for reversible contributing factors of cognitive impairment and optimally treatment whenever possible [57]. Moreover, it is recommended that patients with signs of cognitive dysfunction are referred for assessment and rehabilitation, including group cognitive training if available [57].

2.2.2.7 Altered Body Image and Sexual Dysfunction

Other less recognized effects of chemotherapy include sexual dysfunction.

Surgical interventions with mastectomy (with or without reconstruction) and lumpectomy have been associated with altered body image and sexuality [58, 59]. Women who undergo radiation therapy may be influenced by radiation tattoos, changes in breast sensation, fatigue, or arm mobility [60]. ASCO guidelines recommend that primary care clinicians should assess for patient body image/appearance concerns and should offer the option of adaptive devices (e.g., breast prostheses) and/or surgery when appropriate [57]. Chemotherapy has also been associated with sexual dysfunction [61].

For the assessment of sexual dysfunction, three scales (Arizona Sexual Experience Scale, Female Sexual Functioning Index [FSFI], and Sexual Problems Scale) were identified as most closely meeting criteria for acceptable psychometric properties [62]. In a study of 100 women, sexual dysfunction attributed to breast cancer or its treatment was assessed via the FSFI questionnaire and defined as an FSFI score <26 [63]. Sexual dysfunction was reported by 75% of the responders, and in 83% of cases, patients attributed their sexual dysfunction to chemotherapy [63]. Other contributors to sexual dysfunction were felt to include anxiety by 83% of the patients and change in relationship with a partner by 46% [63]. Assessment of sexual symptoms throughout treatment and beyond may facilitate the use of potential and specific interventions [63]. Moreover, it is recommended that primary care clinicians should assess for reversible contributing factors to sexual dysfunction and treat, when appropriate [57].

For the treatment of sexual dysfunction, patients should be referred for psychoeducational support, group therapy, sexual counseling, marital counseling, or intensive psychotherapy when appropriate [57]. An ongoing randomized study is investigating the efficacy of an internet-based cognitive behavioral therapy program in alleviating problems with sexuality and intimacy in women who have been treated for breast cancer [64].

Non-hormonal, water-based lubricants and moisturizers for vaginal dryness should be offered [57]. For breast cancer survivors with menopausal dyspareunia, the application of liquid lidocaine compresses to the vulvar vestibule before penetration showed to be effective for comfortable intercourse [65].

2.2.2.8 Fertility

In premenopausal patients, the use of chemotherapy may be associated with the occurrence of premature ovarian insufficiency, consisting in temporary or permanent amenorrhea; even in the presence or resumed regular menstrual activity after chemotherapy, women are still at risk of developing early menopause due to the damage of cytotoxic therapy to their ovarian reserve [66]. The development of treatment-induced premature ovarian insufficiency negatively impacts on global health of young breast cancer survivors being associated with several side effects (e.g., hot flashes, sweats, breast pain or sensitivity, vaginal dryness, vaginal discharge, lack of sexual desire, and weight gain) [67]. Moreover, the loss of ovarian function is strongly associated with the risk of infertility: fertility issues represent a major concern for young women with breast cancer being associated with a significant concern that can cause distress and can also affect treatment-related decisions [68].

All young patients interested in fertility preservation should be referred for oncofertility counseling, in a multidisciplinary environment, as soon as possible after diagnosis [69–72].

Several options for potential preservation of fertility exist for breast cancer patients: embryo or oocyte cryopreservation, cryopreservation of ovarian tissue, and temporary ovarian suppression with luteinizing hormone-releasing hormone agonists administered during chemotherapy [73]. These strategies are discussed in Chap. 13.

2.2.2.9 Secondary Malignancies

Adjuvant chemotherapy with anthracyclines and/or alkylating agents has been implicated as a risk factor for the development of secondary malignancies, mostly acute myeloid leukemia (AML) with or without preleukemic myelodysplastic syndrome (MDS). The risk is proportional to cumulative dose [21]. Patients who receive standard doses of anthracycline-based chemotherapy have a relatively low risk of AML/MDS; the benefit associated with this treatment in terms of reduction in breast cancer recurrence and mortality is appreciably high and often vastly overrides the minimum risk of developing a second malignancy [21].

In a meta-analysis of 19 randomized controlled trials (N = 9796) of patients treated with adjuvant epirubicin in early breast cancer, the 8-year cumulative probability of AML/MDS was 0.55% (95% CI 0.33–0.78%), and the risk increased in relation to the dose of epirubicin [74]. Similarly, the risk of AML/MDS after standard dose of doxorubicin seems to be less than 1% [75].

It has been observed that survivors of breast cancer who develop treatment-related leukemia tend to have personal and family histories suggestive of inherited cancer susceptibility and frequently carry germline mutations in breast cancer susceptibility genes [76].

Prophylactic G-CSF should be used as a supportive treatment in patients receiving a chemotherapy regimen with high risk (>20%) of febrile neutropenia or regimens associated with an intermediate risk (10–20%) of febrile neutropenia in the presence of patient- or disease-related risk factors that may increase the overall risk of developing this side effect and finally to support dose-dense chemotherapy [7, 12]. The use of G-CSF is associated with an increased risk of AML/MDS (absolute risk increase 0.41%; 95% CI, 0.10–0.72%; P = 0.009; relative risk [RR] 1.92; 95% CI, 1.19–3.07; P = 0.007) [77]. However, all-cause mortality is decreased in patients receiving chemotherapy with G-CSF support (due to greater chemotherapy dose intensity and fewer complications) [77].

2.3 Endocrine Therapies

Endocrine therapy is the first "targeted" medical treatment in oncology with antitumor activity restricted to patients whose breast tumors express estrogen receptors (ER) and/or progesterone receptors (PR). It is an extremely powerful treatment modality prescribed to two thirds of the breast cancer population, both in advanced and early disease stages.

It is also recognized as an effective prevention approach of the disease but with a low uptake by women at risk in view of its side effects.

One distinguishes three main classes of endocrine agents, based on their mechanism of action:

(a) The SERMs—or selective estrogen receptor modulators—which bind the ER and interfere with its transcriptional activity

(b) The selective estrogen receptor downregulator fulvestrant—which binds the ER and accelerates its destruction
(c) The aromatase inhibitors—which inhibit the enzyme aromatase and, as a result, profoundly reduce estrogen levels in postmenopausal women

Tamoxifen is the parent compound in the family of selective estrogen receptor modulators (SERM) and has been in clinical use for more than 30 years. The recommended dose of tamoxifen is 20 mg daily, and its duration in the adjuvant setting is 5 years; extension beyond 5 years modestly improves disease-free survival and breast cancer mortality [78, 79]. Tamoxifen acts both as an estrogen agonist and antagonist depending on the target organ. In breast tumor tissue, it is able to competitively block the proliferative effect of estrogen. Conversely it displays estrogenic effects in the bone, uterus, and cardiovascular system.

Fulvestrant (Faslodex) downregulates the estrogen receptor and lacks the partial agonist effects of tamoxifen. Its clinical use is limited to the advanced setting. The currently approved dose of fulvestrant is 500 mg by intramuscular injections on days 0, 14, and 28, followed by recycling every 28 days thereafter [80].

Third-generation *aromatase inhibitors*—AI—(exemestane, anastrozole, and letrozole) have shown superior control of advanced breast cancer when compared to tamoxifen but no significant impact on overall survival [81–83]. Adjuvant treatment with AIs in postmenopausal patients has been consistently associated with decreased risks of disease recurrence when used either upfront or after 2–3 years of tamoxifen, compared to tamoxifen alone given for 5 years [84]. Nowadays, AIs are prescribed today to many postmenopausal patients newly diagnosed with hormone receptor-positive operable breast cancer particularly when their risk of relapse is moderate to high. Their optimal timing and duration have not yet been fully elucidated.

In premenopausal patients, the ABCSG-12 trial showed that the combination of anastrozole and ovarian suppression for 3 years was associated with no difference in disease-free survival and a significantly worse overall survival as compared to tamoxifen plus ovarian function suppression [85]. Exemestane and ovarian suppression for 5 years slightly increased disease-free survival compared to tamoxifen and ovarian suppression in the combined analysis of the SOFT and TEXT trials (absolute benefit of 4% at 5 years) [86]. The overall survival results are not yet mature [86].

Data on the relative efficacy and toxicity of different AIs are beginning to emerge: the NCIC CTG MA.27 trial compared adjuvant exemestane (steroidal AI) and anastrozole (nonsteroidal AI) in postmenopausal women with hormone receptor-positive primary breast cancer and showed similar control of the disease with slightly different side effect profiles [87]. Hypertriglyceridemia and hypercholesterolemia were less likely to occur in patients receiving exemestane, and patients taking exemestane were less likely to report a new diagnosis of osteoporosis [87]. Despite the higher incidence of osteoporosis with anastrozole, fracture rates were similar [87]. Musculoskeletal and vasomotor symptoms were similar in both groups [87]. The publication of the results of the "FACE" trial comparing letrozole and anastrozole in about 4000 women with ER-positive, node-positive breast cancer is awaited.

Adverse effects of the three families of endocrine agents share common features—such as hot flushes related to estrogen deprivation—but also show marked differences, largely explained by the distinct mechanisms of action. These differences have been best studied in the very large adjuvant clinical trials that have compared, in more than 40,000 women, tamoxifen to AIs or one AI versus another (2 trials of a few thousand patients) [84]. For fulvestrant, comparisons to either tamoxifen or AIs are available only in the context of smaller randomized metastatic trials involving a lower number of patients [88–91]. These toxicities are described in Table 2.3 and are discussed in more detail below.

2.3.1 Gynecological Side Effects

SERMs display estrogen agonist effects in some organs such as the uterus. Endometrial abnormalities include benign hyperplasia, benign uterine polyps, or endometrial carcinoma. The risk of endometrial cancer with long-term tamoxifen use is low and extends several years beyond treatment completion. To note that 10 years of tamoxifen practically doubles the risk to develop endometrial cancer compared to 5 years (3.1% vs 1.6%) [78]. Fewer gynecological symptoms have been reported with fulvestrant than with tamoxifen (3.9% vs 6.3%) [90]. AIs are devoid of endometrial side effects, and it is therefore not surprising that gynecological symptoms are significantly less common in patients receiving upfront AI compared to those receiving 5 years of tamoxifen in ATAC and BIG 1-98 trials [92, 93]. Fewer gynecological symptoms are also reported in trials in which women take 2–3 years of tamoxifen in view of a switch to an AI compared to women who have pursued tamoxifen for 5 years [93, 94]. Currently, according to the recommendations of the American College of Obstetricians and Gynecologists, neither active screening by transvaginal ultrasound (TVS) nor endometrial biopsies are recommended in asymptomatic women on tamoxifen [95]. The routine follow-up of endometrial changes with TVS in 237 women taking tamoxifen found a high false-positive rate of the procedure even with a cutoff value at 10 mm of endometrial thickness to trigger biopsy, and the price to pay was a high iatrogenic complication rate. To diagnose only one endometrial cancer in asymptomatic patients, fifty-two women had to undergo hysteroscopy and curettage resulting in four uterine perforations [96]. Therefore routine annual gynecologic examination is the attitude of choice in the monitoring of women on tamoxifen. Patients should be educated to report any abnormal vaginal bleeding, discharge, or spotting. Although endometrial cancer is a rare event, it can occasionally be fatal. Therefore, every abnormal gynecologic symptom should be investigated by diagnostic hysteroscopy and endometrial biopsy. If atypical endometrial hyperplasia develops, tamoxifen treatment should be discontinued [97]. AIs in this case are an alternative for postmenopausal women, but they induce vaginal dryness contributing to the loss of libido. Non-hormonal lubricants may be used to release symptoms. Due to the risk of systemic absorption, estrogen-containing vaginal preparations should be avoided.

Table 2.3 Side effects of endocrine therapies

Drug usual dose and schedule	Context of prescription	Minimal requirements for prescription	Most common side effects vs rare ones	Special tests (if any) to monitor side effects	Recommendations for the prevention/ management of side effects
Tamoxifen 20 mg PO daily	Prevention (neo)adjuvant metastatic	Presence of hormone receptors in primary tumor	Hot flushes		Consider antidepressants such as venlafaxine or the antihypertensive centrally acting alpha-adrenergic agonist, clonidine
			Mood disturbances		Consider psychological support
			Menstrual cycle perturbations		Consider IUD in young and fertile women
			Fatty liver		Monitor liver function tests from time to time
			Thromboembolic events		Interrupt tamoxifen a few weeks in case of surgery/immobilization. Consider prophylactic anticoagulation if ≥4 h airplane travel
			Gynecological events: vaginal discharge, uterine polyps, and endometrial abnormalities (hyperplasia, cancer)	Transvaginal ultrasonography is not recommended for active screening	Routine annual gynecologic evaluation. Any abnormal vaginal bleeding should be investigated with diagnostic hysteroscopy and endometrial biopsy
			Cataract		Instruct patient to report visual disturbances
Usual dose and schedule	Context of prescription	Minimal requirements for prescription	Most common side effects vs rare ones	Special tests (if any) to monitor side effects	Recommendations for the prevention/ management of side effects

Aromatase inhibitors – Anastrozole 1 mg PO daily – Letrozole 2.5 mg PO daily – Exemestane 25 mg PO daily	Adjuvant metastatic	Presence of hormone receptors in primary tumor	Arthralgias and myalgia		Consider pain and anti-inflammatory medications. If ineffective consider shift to another AI. Anecdotal reports that glucosamine may help. Encourage patients to do regular physical exercise. For patients experiencing disabling symptoms, consider changing to tamoxifen
			Bone loss	Bone mineral density measurement by DXA every 1–2 years	Advice on lifestyle changes. Implementation of calcium and vitamin D supplementation to prevent bone health impairment. Consider bisphosphonate therapy in osteoporotic patients but also in the case of osteopenia if risk factors for bone fracture are present such as age older than 65 years, low BMI, family history of hip fracture, personal history of fracture under 50 years, current use of corticosteroids or current smoking
			Cardiovascular events		Regular screening for cardiovascular risk factors such as hypertension and hypercholesterolemia
			Hypercholesterolemia		Regular lipid profile monitoring. Consider statins in the case of increased serum cholesterol level
			Hot flushes		Consider antidepressants such as venlafaxine or the centrally acting alpha-adrenergic agonist, clonidine
			Vaginal dryness/loss of libido		Nonhormonal local lubricants can temporarily release symptoms. Estrogen-containing vaginal preparations should be avoided
			Cognitive impairment		Instruct patients to report any memory disorder or impairments of processing speed

(continued)

Table 2.3 (continued)

Drug usual dose and schedule	Context of prescription	Minimal requirements for prescription	Most common side effects vs rare ones	Special tests (if any) to monitor side effects	Recommendations for the prevention/ management of side effects
Usual dose and schedule	Context of prescription	Minimal requirements for prescription	Most common side effects vs rare ones	Special tests (if any) to monitor side effects	Recommendations for the prevention/ management of side effects
Fulvestrant 500 mg IM d0–d15–d28 then every 4 weeks	Metastatic	Presence of hormone receptors in primary tumor	Injection-site reactions		Use the proper injection technique, and rotate injection site. Consider local ice or cold compresses if local complications occur
			Joint disorders (arthralgia)		Consider pain and anti-inflammatory medications. Encourage patients to do regular physical exercise
			Thromboembolic events		Interrupt fulvestrant a few weeks in case of surgery/immobilization. Consider prophylactic anticoagulation if ≥4 h airplane travel
			Hot flushes		Consider antidepressants such as venlafaxine or the centrally acting alpha-adrenergic agonist, clonidine

2.3.2 Thromboembolic Disease

Several adjuvant and prevention trials have demonstrated an increased risk for venous thromboembolic events during tamoxifen treatment. With adjuvant upfront AI treatment, the frequency of thromboembolic complications is significantly lower compared to patients treated with tamoxifen [92–94, 98]. At higher risk to develop this severe toxicity are women who need a prolonged immobilization for a surgical intervention: in this case a treatment interruption for several weeks is highly recommended. Additionally among patients diagnosed with tamoxifen-related venous thrombosis, the incidence of factor V Leiden mutation is nearly five times higher than in those who do not develop this toxicity. Therefore women harboring this genetic alteration are not candidates for tamoxifen [99]. A detailed personal and familial medical history in search of thromboembolic events is mandatory prior to initiating a SERM or fulvestrant. A complete blood coagulation work-up should follow in case of doubt and should consist in the following screening blood tests: resistance to activated protein C, antiphospholipid antibodies, antithrombin, and proteins C and S as well as genotyping for factor V and prothrombin can be useful.

In the head-to-head comparison between fulvestrant and tamoxifen, the risk of developing venous thromboembolic events was comparable with both treatments [90]. Thus in women treated with fulvestrant, the same preventive measures should be considered than in those who are treated with tamoxifen.

2.3.3 Hot Flashes

Vasomotor symptoms are frequent complications consecutive to estrogen depletion in women treated for breast cancer, producing impairment of quality of life and leading to non-compliance. This adverse event seems to occur slightly more often in patients treated with tamoxifen compared to aromatase inhibitors in adjuvant trials and compared to fulvestrant in treatment of metastatic disease. The reported incidence across different studies is around 35–40% [92–94, 98]. In premenopausal patients undergoing ovarian suppression combined with tamoxifen [100] or AI [86], the incidence is much higher, around 90%. Successful management is challenging. Non-estrogenic pharmacological interventions such as the selective serotonin-norepinephrine reuptake inhibitor venlafaxine at 75 mg/day and the antihypertensive centrally acting adrenergic agonist, clonidine, at 0.1 mg/day show some efficacy in reducing hot flashes [101].

2.3.4 Eye Problems

The rate of cataract was significantly increased by tamoxifen compared to placebo in the large NSABP P-1 preventive study. This complication occurred in 2.77% of women treated with tamoxifen, while the incidence of cataract surgery was 1% [102]. Women should be asked to report any visual abnormality, and

ophthalmological investigations should be ordered in symptomatic patients. Four cases of retinopathy were reported in 63 patients prospectively followed for ocular toxicity. Retinal opacities were not reversible with tamoxifen withdrawal [103].

2.3.5 Musculoskeletal Pain

According to toxicity data of multiple adjuvant trials, joint pain emerged as a prominent side effect of aromatase inhibitors, seen in about 35% of women and representing the first cause of non-compliance. In the exemestane arm of the SOFT and TEXT trials, more than 80% of premenopausal patients reported joint pain [86]. Patients should be reassured and told that symptoms can be managed, can improve over time, and are reversible upon treatment discontinuation. Patients should be encouraged to have regular physical exercise. Pharmacological interventions such as nonsteroidal anti-inflammatory drugs (NSAIDs), cyclooxygenase-2 inhibitors, and the use of pain medications such as opioids can help to release symptoms [104]. A shift to another AI can be considered if pain treatment is unsuccessful and, in the case of persisting disabling symptoms, tamoxifen might still be proposed as a suitable alternative.

2.3.6 Bone Loss

Estrogen deprivation at almost undetectable levels by AIs leads to increased bone loss and an increased risk of fractures. This is in sharp contrast with the protective effect of SERMs on bone. In the ATAC and TEAM trials, the incidence of osteoporosis ranged from 10 to 11% among women treated with 5 years of anastrozole or exemestane [92, 98]. In the sequential arms of the IES and TEAM studies (tamoxifen followed by 2–3 years of exemestane), only 6% of patients experienced bone loss [94, 98]. The incidence is higher in premenopausal patents treated with both exemestane and ovarian suppression (38%).

The reported fracture rate with 5 years of AI in the adjuvant setting ranges from 5 to 11% [92, 93, 98]. Regarding fulvestrant, osteoporosis was only reported in one patient receiving the dose of 500 mg [80].

It is highly recommended that all women starting treatment with an AI undergo a bone mineral density (BMD) measurement by DEXA (dual-energy X-ray absorptiometry) and a global assessment of risk factors for developing osteoporotic fractures such as age older than 65 years, low BMI, family history of hip fracture, personal history of fracture under 50 years, current corticosteroid use, current smoking, and increased alcohol intake [105]. Those patients presenting baseline osteopenia or classified “high risk” should have their BMD monitored every 1–2 years. The implementation of lifestyle changes and adequate supplementation of vitamin D (≥800 UI/day) and calcium (1200–1500 mg/day) should be considered to preserve bone health [106]. Current ASCO guidelines recommend the initiation

of bisphosphonate treatment in the case of osteoporosis (T score $\leq$2.5) [105]. A European panel of experts recommended that bisphosphonates should be considered as part of routine clinical practice for preventing bone loss due to anticancer treatments in all patients with a T score of $\leq$2.0 or $\geq$2 clinical risk factors for fracture [107].

Lately, twice-yearly administration of 60 mg of denosumab, a fully human antibody against RANK ligand, was associated with a significant increase of BMD in women receiving adjuvant aromatase inhibitor [108, 109].

2.3.7 Cardiovascular Events

Cardiovascular events include myocardial ischemia and strokes. Monitoring of the cardiovascular safety of aromatase inhibitors has been poorly standardized in trials, and, in addition, data might still be immature. Individual adjuvant trials did not identify a higher risk of developing cardiac events with upfront AI compared to tamoxifen alone [92, 93]. However, a meta-analysis of 7 adjuvant trials including 30,023 patients found that the risk of cardiovascular disease (including myocardial infarction, angina, and cardiac failure) was significantly higher with aromatase inhibitors upfront compared to 5 years of tamoxifen or the switching strategy (4.2% in the aromatase inhibitor group versus 3.4% in tamoxifen group, OR = 1.26, 95% CI = 1.10–1.43, $p < 0.001$) [110]. There is no evidence that tamoxifen increases the risk of ischemic heart disease compared to placebo in the NSABP-P1 trial. Severe coronary syndromes ranged from 0.94 to 1.12% in this study [102]. In the joint analysis of SOFT and TEXT trials, only 0.7% of patients treated with exemestane and ovarian suppression experienced a cardiac event [86]. The increase in serum cholesterol level is a well-known phenomenon during AI therapy and could be one parameter for the increased risk to develop myocardial ischemia. Therefore a regular screening for cardiovascular risk factors is highly recommended in women treated with aromatase inhibitors. The prescription of an AI in postmenopausal patients with a personal history of ischemic heart disease should be considered after a careful evaluation of the individual risk of breast cancer recurrence, and the sequential strategy might be preferred over upfront AI, especially for women at low or moderate risk of relapse.

2.3.8 Cognitive Dysfunction

Data from large adjuvant trials regarding cognitive function is quite limited and conflicting. However a BIG 1-98 substudy examined differences in cognitive function associated with each endocrine treatment after 5 years of treatment and 1 year after treatment cessation. Patients taking letrozole had better overall composite cognitive scores than those treated with tamoxifen [111]. An improvement was noticed after treatment withdrawal. A cross-sectional study from the TEAM trial is

consistent with these findings, suggesting a better cognitive function with exemestane than tamoxifen [112]. In young premenopausal patients, a small sub-analysis of the SOFT study provided no evidence that the addition of ovarian function suppression to adjuvant oral endocrine therapy with tamoxifen or exemestane substantially affects global cognitive function [113]. These data are still limited and immature to draw firm conclusions and to make recommendations on how cognitive function impairment should be monitored during long-term hormonal treatment.

2.4 Targeted Agents

Trastuzumab (Herceptin®) is a monoclonal IgG1 class humanized murine antibody that binds the extracellular portion of the HER2 transmembrane receptor [114]. Since its launch in 1998, trastuzumab has become the backbone of care of HER2-positive breast cancer [115], both in the metastatic and early disease settings [116–121].

In 2007, a second targeted agent was approved for the treatment of HER2-positive breast cancer: lapatinib (Tykerb®) [115]. This oral small molecule targets the tyrosine kinase activity of HER2 and epidermal growth factor receptor (EGFR or HER1). It is approved in combination with capecitabine or letrozole in the treatment of HER2-positive metastatic breast cancer and has been also evaluated in clinical trials in the (neo) adjuvant setting [122, 123].

There is a growing list of novel anti-HER2 agents showing promising activity in women with HER2-positive disease.

Pertuzumab is a monoclonal antibody that binds to the HER2 dimerization domain [124] and, as a result, inhibits the formation of HER2 dimers, including the HER2-HER3 heterodimer. Pertuzumab is now approved in combination with taxane-based chemotherapy and trastuzumab in the neoadjuvant setting and for first-line treatment of metastatic HER2-positive breast cancer [115] following the results of two large phase III studies [125–127].

Trastuzumab-DM1 is an antibody drug conjugate linking trastuzumab with the fungal toxin maytansine (DM-1) that specifically delivers the anti-microtubule agent (DM1) to HER2-positive cells [128]. T-DM1 has received regulatory approval for the treatment of HER2-positive metastatic breast cancer [115] following the results of two phase III trials [129, 130]. The toxicity profile of T-DM1 was favorable versus the standard-of-care comparators.

Neratinib [HKI-272] is a potent irreversible pan-HER kinase inhibitor with efficacy shown in HER2-positive metastatic breast cancer [131]. A large phase III trial in women with HER2-positive early breast cancer has shown a very modest improvement in invasive disease-free survival with neratinib versus placebo as extended adjuvant treatment following 1 year of trastuzumab [132].

Bevacizumab (Avastin®) is approved for the treatment of metastatic breast cancer [133]. Bevacizumab is a humanized monoclonal antibody against vascular endothelial growth factor (VEGF), which is a key angiogenic factor [134]. Bevacizumab is approved by EMA for the first-line treatment of metastatic breast cancer in combination with paclitaxel or capecitabine.

Novel agents have gained regulatory approvals for the treatment of ER-positive metastatic breast cancer in combination with endocrine therapy. Everolimus, a sirolimus derivative that inhibits mTOR through allosteric binding to mTORC1, was approved in combination with exemestane for the treatment of ER-positive metastatic breast cancer after the failure of a nonsteroidal aromatase inhibitor following the positive results of the BOLERO-2 phase III clinical trial [135].

Palbociclib, an orally bioavailable small-molecule inhibitor of CDK4 and CDK6, with a high level of selectivity for CDK4 and CDK6 over other cyclin-dependent kinases, is approved for the first-line treatment of ER-positive metastatic breast cancer in combination with letrozole following the results of the PALOMA-1 phase II trial [136]. Palbociclib is FDA- and EMA-approved in combination with fulvestrant after disease progression on endocrine therapy following the results of the PALOMA-3 phase III clinical trial [137].

Targeted therapies have toxicity profiles that differ from those of traditional cytotoxic chemotherapy. While the concept of specifically targeting malignant cells implies sparing normal cells, targeted agents have proved their share of side effects, often leading to dose reduction, treatment delays, and interruption. Side effects of targeted agents can be divided into "class"-specific and "agent"-specific.

Monoclonal antibodies are known to generate immediate infusion reactions, but improvement in biotechnology has led to a significant decrease in such events.

Small-molecule inhibitors often cause diarrhea and skin rash. They are mostly metabolized by cytochrome P450 3A4 and therefore are subject to multiple drug interactions contrary to monoclonal antibodies that do not undergo hepatic metabolism.

All anti-HER2 agents can potentially cause left ventricular myocardial dysfunction, and caution is required when they are used in combination or sequence with cardiotoxic chemotherapy.

Toxicity of bevacizumab is typical of agents targeting the VEGF pathway and includes hypertension, bleeding, thrombosis, impaired wound healing, and to a less extent myocardial dysfunction.

Table 2.4 summarizes the indications of targeted agents used in the treatment of breast cancer [132, 133, 138–159], as well as major side effects, and monitoring tests. Management algorithms for some key toxicities are presented in Figs. 2.1, 2.2, 2.3, and 2.4.

Table 2.4 Side effects of targeted agents

Drug usual dose and schedule	Context and minimal requirements for prescription	Most common side effects vs rare ones	Incidence	Special tests (if any) to monitor side effects	Recommendations for the prevention/ management of side effects
Bevacizumab	Metastatic breast cancer in combination with paclitaxel or capecitabine	Hypertension	0.8–17.9%. Higher incidence with 15 vs 7.5 mg/kg	Blood pressure monitoring every 2–3 weeks during treatment. Target BP = 135/85 for cancer patients with comorbidities as kidney disease	Treat with appropriate antihypertensive therapy. Beware of interactions: nifedipine (use cautiously), verapamil, diltiazem, and CYP3A4 inhibitors (contraindicated). ACE inhibitors preferred mainly because of proteinuria. Discontinue bevacizumab for hypertensive crisis or hypertensive encephalopathy Hold bevacizumab for severe hypertension not controlled with medical management Continue to monitor blood pressure at regular intervals after discontinuation of bevacizumab
		Proteinuria	0.8–3.9%	Urine dipstick analysis for proteinuria before each administration 24-h urine collection if urine dipstick 2+ or more for proteinuria	Discontinue bevacizumab for nephrotic syndrome Hold bevacizumab for moderate to severe proteinuria (≥2 g/24 h) No data on bevacizumab administration in patients with moderate proteinuria
		Wound-healing complications	0.4–1.5%	Clinical appreciation	Hold bevacizumab 28 days before elective surgery Treat with bevacizumab 28 days after surgery if surgical wound is fully healed Exclude patients with non-healing wounds, active gastric ulcers, and bone fractures
		Gastrointestinal perforation	0.4–2.5%	Mostly dependent on site of disease	Exclude patients with abdominal fistula, GIP, or intra-abdominal abscess in the last 6 months Discontinue bevacizumab in case of GIP

Drug	Context and minimal requirements for prescription	Most common side effects vs rare ones	Incidence	Special tests (if any) to monitor side effects	Recommendations for the prevention/ management of side effects
Bevacizumab	Metastatic breast cancer in combination with paclitaxel or capecitabine	Bleeding/hemorrhage	0.4–5.4%	Clinical appreciation CBC	Do not exclude patients with CNS metastases Discontinue bevacizumab for serious bleeding events Anticoagulation should not be contraindicated Low-dose aspirin should not be contraindicated
		Thromboembolic events	0.7–6.5% (ATE and VTE combined)	Mainly arterial thrombotic events	Prophylactic low-dose aspirin for high-risk patients (≥65 years old, previous arterial thrombosis or emboli) Manage by anticoagulants Discontinue bevacizumab after severe arterial thrombotic events
		Cardiovascular events (CHF)	1.6%. No differences seen with different doses or concomitant chemotherapy agents	Echocardiography, MUGA scintigraphy every 3–4 months and 6–8 months after completion of treatment. Studies on radioactive tracers, serum biomarkers, and genetic polymorphisms are ongoing	Discontinue bevacizumab. Start ACE inhibitors or ARBs (aldosterone receptors blockers) + beta-blockers + diuretics
		Osteonecrosis of the jaw	0.3–0.4%. Higher in patients treated with bisphosphonates. Bev does not appear to elevate the risk compared to chemotherapy	Clinical appreciation, X-ray, CT scan	

(continued)

Table 2.4 (continued)

Drug usual dose and schedule	Context and minimal requirements for prescription	Most common side effects vs rare ones	Incidence	Special tests (if any) to monitor side effects	Recommendations for the prevention/ management of side effects
Trastuzumab	HER2-positive (IHC 3+ or IHC 2+ and FISH ratio >2.2) breast cancer in the neo-adjuvant, adjuvant, and metastatic settings	Asymptomatic left ventricular systolic dysfunction	11–17% in the metastatic setting when combined with chemotherapy 0–18.6% in the adjuvant setting. 4% when combined with endocrine treatment	Echocardiography, MUGA scintigraphy every 12 weeks on treatment. Studies on radioactive tracers, serum biomarkers and genetic polymorphisms are ongoing	Start ACE inhibitors. See algorithm of management
		Symptomatic CHF	2% in the metastatic setting when combined with taxane, and 16% when combined with anthracyclines. 0–3.8% in the adjuvant setting. <1% when combined with endocrine treatment. 4% with single-agent treatment in heavily pretreated patients		
		Infusion reactions	Mild to moderate reactions in 25–38% of first infusions. <1% severe events (anaphylaxis). Includes fever, chills, and, on occasion, nausea, vomiting, pain, headache, dizziness, dyspnea, rash, and asthenia	Clinical assessment. Symptoms usually occur during or within 24 h of Herceptin administration	Interrupt infusion for dyspnea or clinically significant hypotension Monitor patients until symptoms completely resolve Discontinue for infusion reactions manifesting as anaphylaxis, angioedema, interstitial pneumonitis, or acute respiratory distress syndrome. Strongly consider permanent discontinuation in all patients with severe infusion reactions. Slow infusion rate. Administer acetaminophen, diphenhydramine, and/or meperidine, corticosteroids

Drug	Context and minimal requirements for prescription	Most common side effects vs rare ones	Incidence	Special tests (if any) to monitor side effects	Recommendations for the prevention/ management of side effects
Pertuzumab	HER2-positive (IHC 3+ or IHC 2+ and FISH ratio >2.2) breast cancer in the neoadjuvant and metastatic settings	Asymptomatic left ventricular systolic dysfunction	6.9% with pertuzumab alone, 3.4% with pertuzumab in combination with non-anthracycline chemotherapy, 6.5% with pertuzumab in combination with trastuzumab	Echocardiography, MUGA scintigraphy every 12 weeks on treatment	See algorithm of treatment
		Symptomatic CHF	0.3% with pertuzumab alone, 1.1% with pertuzumab in combination with non-anthracycline chemotherapy, 1.1% with pertuzumab in combination with trastuzumab		
		Diarrhea	51% all grades and 5.4–7.3% grade 3. 64% when given with trastuzumab	Patient symptoms. NCI-CTC grading	Supportive measures Loperamide if necessary
		Nausea	24–27%, no grade 3 or 4. 27% when given with trastuzumab	Patient symptoms	Anti-emetics at the discretion of the treating physician
		Fatigue	22–24%, 2.4% grade 3. 33% when given with trastuzumab	Patient symptoms	
		Rash including allergic reaction	20%, no grade 3 or 4	Clinical complaint	
		Vomiting	15%, 2.5% grade 3	Patient symptoms	Antiemetics at the discretion of the treating physician

(continued)

Table 2.4 (continued)

Drug usual dose and schedule	Context and minimal requirements for prescription	Most common side effects vs rare ones	Incidence	Special tests (if any) to monitor side effects	Recommendations for the prevention/ management of side effects
T-DM1	HER2-positive (IHC 3+ or IHC 2+ and FISH ratio >2.2) breast cancer in the metastatic setting	Thrombocytopenia	8% grade 3 or 4	CBC before administration	Dose reductions from 3.6 to 3 mg/kg then 2.4 mg/kg
		Fatigue	4.5% grade 3 or 4. 65.2% all grades	Patient symptoms	
		Nausea	0.9% grade 3 or 4. 50.9% all grades		Antiemetics at the discretion of treating physician
		Headache	40.2% grade 1		Common analgesics
		Hypokalemia	8.9% grade 3 or 4. 24.1% all grades	Chemistry before administration	K+ supplementation. Not associated with vomiting, diarrhea, or diuretic use

Drug	Context and minimal requirements for prescription	Most common side effects vs rare ones	Incidence	Special tests (if any) to monitor side effects	Recommendations for the prevention/ management of side effects
Lapatinib	HER2-positive (IHC 3+ or IHC 2+ and FISH ratio >2.2) breast cancer after progression on trastuzumab in the metastatic setting	Diarrhea	19–48% monotherapy, 60% when combined with capecitabine with 13% grade 3/4, 60% when combine with trastuzumab with 9% grade 3, 63% when combined with letrozole	Patient symptoms. NCI-CTC grading	See algorithm of management
		Rash	22–44% depending if single-agent, in combination with chemotherapy or with endocrine therapy. 6% grade 3, no grade 4	Acne-like rash of folliculitis: inflammatory papules and pustules on the face, scalp, chest and back	See algorithm of management. Retinoids not indicated
		Other skin disorders	1–4%	Hair disorders, dry skin, pruritus/urticaria, nail disorders	Emollients, avoid sun
		Hepatotoxicity	1.5% grade 3 ALT elevation. 0.3% serious liver injury with hyperbilirubinemia	Monitoring of LFTs and bilirubin. Association with MHC class II allele HLA-DQA1*02:01	Avoid drug interactions and especially CYP3A4 inducers. Screen for other causes (viral hepatitis, hemochromatosis,etc.). Withdraw treatment
		Left ventricular systolic dysfunction		Echocardiography, MUGA scintigraphy. Cardiac biomarkers (creatinine kinase, troponin, brain natriuretic peptide)	Reversible. See algorithm of management

(continued)

Table 2.4 (continued)

Drug usual dose and schedule	Context and minimal requirements for prescription	Most common side effects vs rare ones	Incidence	Special tests (if any) to monitor side effects	Recommendations for the prevention/ management of side effects
Neratinib	Ongoing trials in HER2-positive (IHC 3+ or IHC 2+ and FISH ratio >2.2) breast cancer	Diarrhea	21% grade 3 or 4. 93% all grades	Patient symptoms. NCI-CTC grading. Blood tests. Stool tests	Grade 3 lasting > 2 days despite optimal medical therapy, or associated with fever or dehydration: hold neratinib until recovery to ≤grade 1 or baseline. Consider prophylactic antidiarrheal medications. If recurrence or if recovery >1 week, reduce dose to 160 mg then 120 mg
		Fatigue	2% grade 3 or 4, 24% all grades	Patient symptoms	Grade 3 and lasting more than 3 days, hold until recovery. Dose reduction if recurrence
		Nausea	2% grade 3 or 4, 36% all grades	Patient symptoms	Anti-emetics at the discretion of treating physician. Hold treatment if grade 3 or more and dose reduction if recurrence
		Vomiting	4% grade 3 or 4, 31% all grades	Patient symptoms	
		Rash	18%, nongrade 3 or 4	Clinical assessment	See rash management algorithm
Afatinib	Ongoing trials in HER2-positive (IHC 3+ or IHC 2+ and FISH ratio >2.2) breast cancer	Diarrhea	87–95%, 18–20% grade 3	Patient symptoms. NCI-CTC grading. Blood tests. Stool tests	See algorithm of management
		Skin reactions	88–95%, 9.8–19% grade 3	Clinical assessment	See algorithm of management

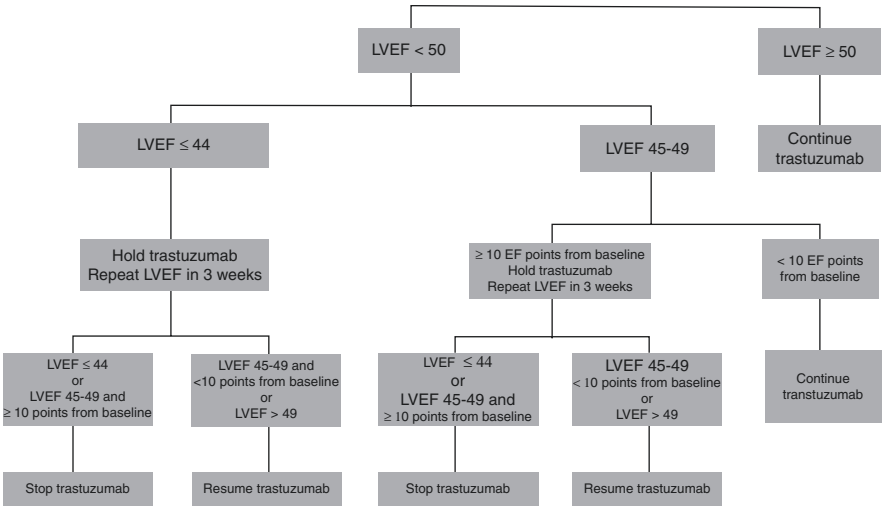

Fig. 2.1 Management of patients showing cardiac dysfunction on trastuzumab [162]

2.4.1 Cardiovascular Toxicity

Cardiac dysfunction was the main adverse event in the first published phase III trial of trastuzumab combined with chemotherapy in the treatment of advanced HER2-positive [116]. Its incidence was as high as 27% in the combination with anthracyclines. This unexpected finding influenced the design of the adjuvant trials that recruited more than 12,000 patients and adopted a sequential administration of anthracyclines and trastuzumab with prospective cardiac function monitoring and stopping rules in the presence of prespecified drops in left ventricular ejection fraction. As a result the observed incidence of cardiotoxicity was low—ranging from 0.4 to 3.6%—and considered acceptable in view of the large reduction in breast cancer relapses and deaths [116–119]. Even though its causes are not fully elucidated, trastuzumab-related left ventricular systolic dysfunction (LVSD) is classified as type 2 chemotherapy-related cardiotoxicity (CRCT). It is mediated by the blockade by trastuzumab of ErbB2-ErbB4 signaling in cardiac myocytes, a pathway thought to play a role in protecting cardiac myocytes from stress conditions. At the opposite of type 1 CRCT that is exemplified by anthracycline-related myocardial damage, trastuzumab LVSD is not dose-related, potentially reversible with medical therapy, and rechallenge is possible [160]. Potential risk factors influencing LVEF deterioration are older age, hypertension, and a baseline LVEF in the lower normal range [24, 116, 161]. Algorithms for initiation of therapy are proposed, as well as algorithms for monitoring and managing cardiac events (see Fig. 2.1) [162]. Reporting of cardiac events in trastuzumab trials prompted close cardiac monitoring of patients on lapatinib and neratinib. Incidence of cardiotoxicity was found to be less with these agents, even in trastuzumab- and anthracycline-pretreated patients.

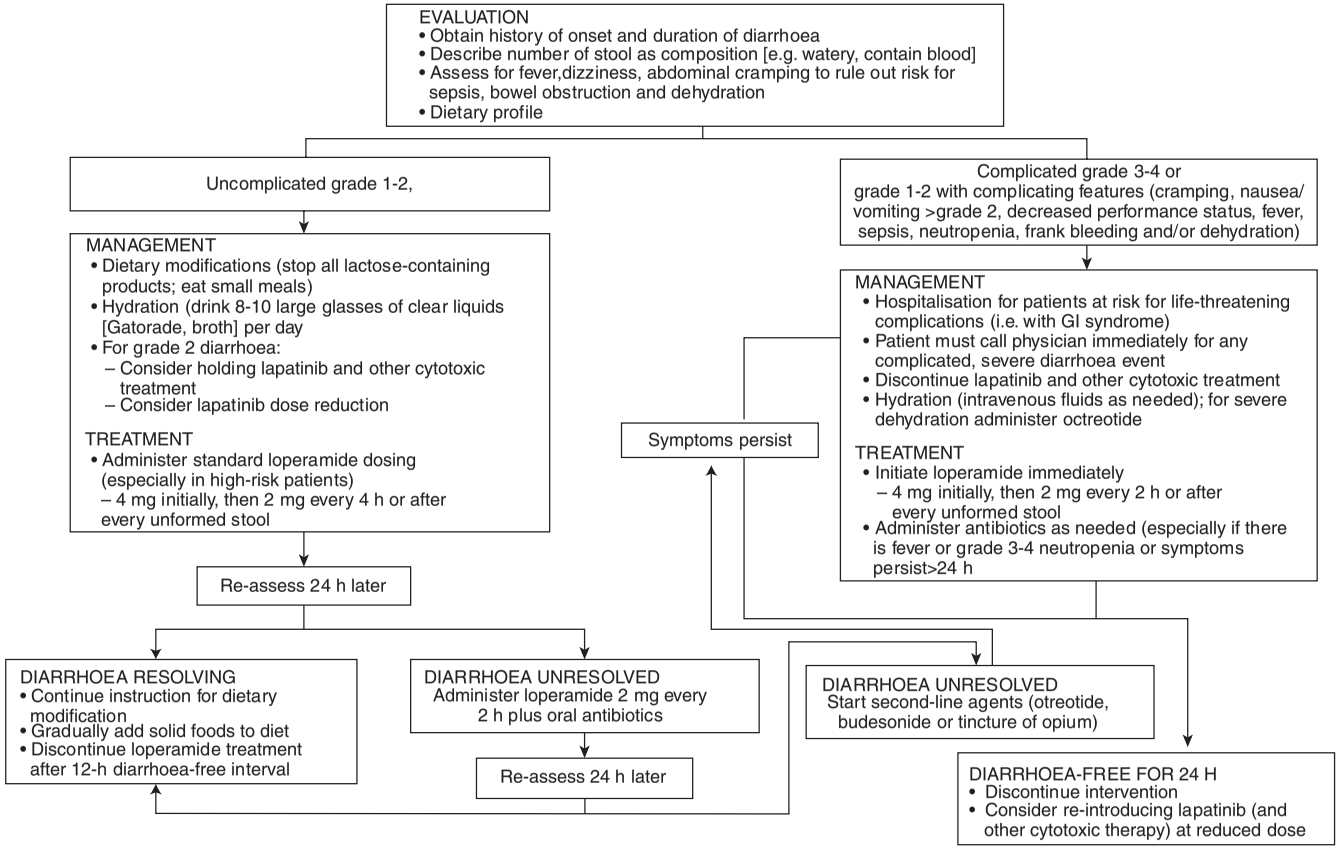

Fig. 2.2 Management of patients experiencing diarrhea on HER1/HER2 tyrosine kinase inhibitors [156]

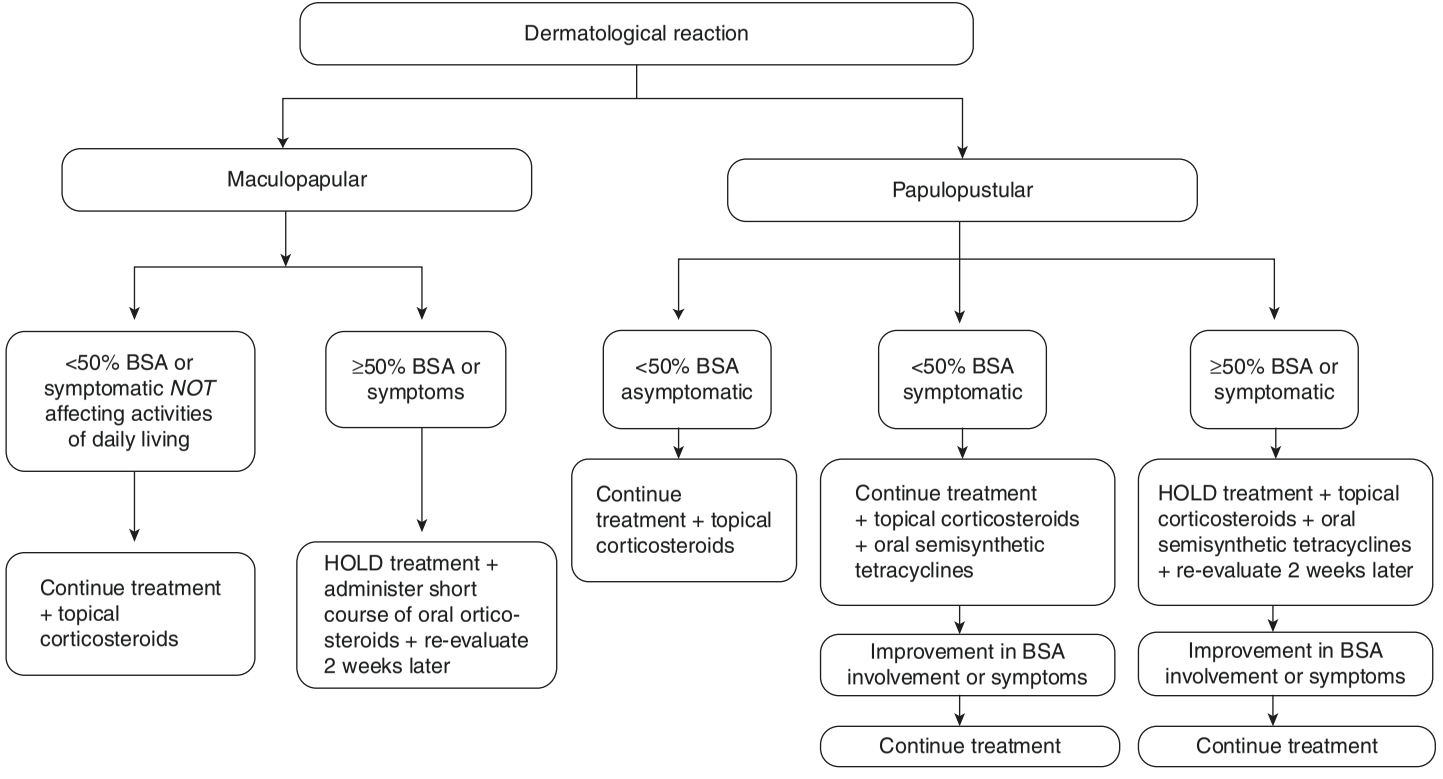

Fig. 2.3 Management of patients experiencing skin toxicity on HER1/HER2 tyrosine kinase inhibitors [156]

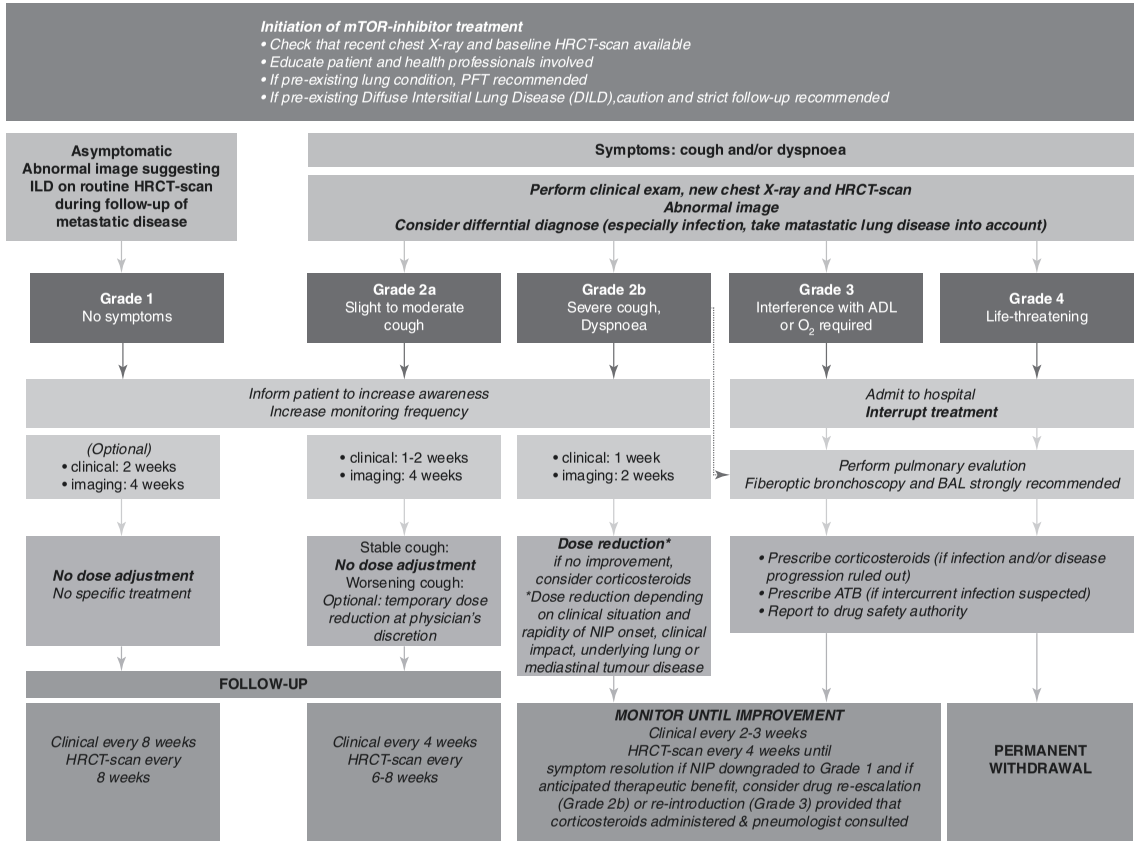

Fig. 2.4 Management of patients experiencing interstitial pneumonitis on mTOR inhibitors [187]

Furthermore, most LVEF decreases were asymptomatic and almost universally reversible [159]. Even though cardiotoxicity of lapatinib seems to be type 2 CRCT as with trastuzumab, theories are being developed to explain the lower incidence and include less potency in inhibiting the HER2/HER4 heterodimer signaling or ATP generation rather than ATP depletion [163].

Left ventricular dysfunction is also a class toxicity of agents targeting the VEGF pathway given that VEGF plays an important role in cardiomyocyte survival after stress or injury [164]. A meta-analysis of bevacizumab trials in metastatic breast cancer demonstrated the increased incidence of left ventricular systolic dysfunction in bevacizumab-treated patients when compared to controls [133]. The overall incidence remains however low and is not dose-dependent nor is it associated with the type of concomitant chemotherapy [133]. Early available data show recovery of cardiac function with interruption of treatment and introduction of cardiac medications [165]. Bevacizumab is also responsible for rare arterial and venous thromboembolic events [147].

2.4.2 Hypertension

Hypertension is a known class effect of antiangiogenic agents. Causal hypotheses include bevacizumab effect on kidney vasculature as well as inhibition of the generation of nitric oxide [166]. Proactive monitoring and management with commonly used antihypertensive medications are required at each cycle. Bevacizumab discontinuation is warranted for uncontrolled hypertension as well as for neurological symptoms (headache, impaired vision, etc.) that can also be caused by the very rare reversible posterior leukoencephalopathy syndrome reported with bevacizumab therapy [140].

2.4.3 Infusion Reactions

Most cancer therapeutics but most certainly monoclonal antibodies carry the risk of infusion reactions. These reactions develop during the infusion or shortly thereafter. They are mostly mild to moderate with various symptoms such as fever, chills, headache, nausea, pruritus, skin rash, etc. Severe cases are characterized by hypotension, urticaria, bronchospasm, and, very rarely, cardiac arrest. Mechanisms by which they occur are immune-mediated: cytokine release and type 1 hypersensitivity reactions mediated by IgE. New technology is helping engineer novel fully humanized monoclonal antibodies in order to minimize immune reactions. Trastuzumab is associated with the highest incidence of infusion reactions among the monoclonal antibodies, but they are largely mild to moderate. Most patients are rechallenged successfully with permanent discontinuation only considered in case of anaphylaxis, angioedema, or acute respiratory distress syndrome.

Incidence of such reactions is lower with bevacizumab and approaches 3.1% in a large adjuvant trial in colorectal cancer [167]. However, there is no data here

concerning the safety of rechallenge in case of a severe reaction. Physicians and nurses should be prepared when these agents are to be infused and epinephrine, corticosteroids, IV antihistamines, bronchodilators, oxygen, and vasopressors should be readily available.

2.4.4 Hepatotoxicity

Hepatobiliary adverse events (AEs) have been reported in patients treated with lapatinib. Hepatotoxicity is predominately hepatocellular injury [157]. A review of data from 16 clinical trials yielded an incidence of 1.5% for grade 3 ALT/AST elevation and 0.3% for liver injury with jaundice meeting the Hy Law's criteria [158]. One study reported 4 withdrawals from treatment and one toxic death by hepatic failure in 138 patients treated with lapatinib [168].

Mechanisms for severe liver toxicity are not fully understood. There might be a role for immune-mediated hypersensitivity reactions, and lapatinib has also been found to be an inactivator of CYP3A4 [169]. Furthermore, recent pharmacogenetic evaluations have identified associations between lapatinib-induced liver injury and four MHC class II alleles. A strong statistical association was observed with HLA-DQA1*02:01 [157]. Management depends on the severity of toxicity. Differential diagnosis must include viral hepatitis, hemochromatosis, alpha-1 antitrypsin deficiency, and liver progressive disease. Clinicians must be aware of drug interactions and avoid CYP3A4 inducers as well as other hepatotoxic drugs such as paracetamol.

Liver toxicity has been reported with other tyrosine kinase inhibitors, and LFT elevations should alert for possible liver toxicity of all small molecules used in breast cancer, including neratinib [170]. Increased AST/ALT have also been reported with T-DM1 in metastatic HER2-positive breast cancer [171].

2.4.5 Gastrointestinal Perforation, Wound-Healing Complications, and Bleeding

They are typical complications of antiangiogenic therapies, but their incidence is low in metastatic breast cancer patients treated with bevacizumab, who rarely present with bulky abdominal disease. Patients with CNS metastases are not excluded anymore from antiangiogenic therapy. It is recommended to hold bevacizumab 4 weeks prior to elective surgery and until at least 28 days after in order to minimize wound-healing complications.

2.4.6 Diarrhea

Diarrhea as an adverse event has been described through the entire spectrum of phase I to III trials with tyrosine kinase inhibitors. It is by far the side effect leading to most dose reductions, treatment discontinuations, and thus decreased efficacy of

these small molecules [170]. Diarrhea with lapatinib appears early, during the first days of treatment (before day 6). It is rarely severe and generally does not need intervention. However, patient monitoring is crucial in order to prevent dehydration and electrolyte imbalance.

TKI-induced diarrhea responds well to conventional antidiarrheal agents. Patients should be encouraged to keep dietary measures and avoid drug interactions. Extreme cases require hospitalization for rehydration, octreotide administration, and possibly antibiotics.

Differential diagnosis includes infectious colitis and malabsorption. Secretory diarrhea is implied by a high content of sodium and chloride and with no presence of mucus, blood, leukocytes, or *Clostridium difficile* toxins. Diarrhea is also commonly described with neratinib. The pathophysiological mechanism is secretory by inhibition of EGFR effects on chloride secretion [172]. Biopsy doesn't usually show mucosal damage, but analysis of tissue from a phase I trial with neratinib revealed mild duodenal mucosal gland dilatation and degeneration in the small intestine [173].

Dual HER2 blockade, using either trastuzumab and lapatinib or trastuzumab and pertuzumab, exacerbates diarrhea, which needs prompt and aggressive treatment. An algorithm (Fig. 2.2) initially developed for management of chemotherapy-induced diarrhea is applicable once diarrhea occurs under pan-ERB TKIs therapy [33].

2.4.7 Skin Rash

Skin rash has been described as a class effect toxicity of ErbB1-targeting agents. As lapatinib targets EGFR as well as HER2, breast cancer patients treated with these agents often develop a characteristic acneiform eruption that may resemble folliculitis. Rash is characterized by inflammatory papules and pustules that are found in areas with pilosebaceous glands such as the face, scalp, chest, and back. The lack of comedones distinguishes this eruption from acne vulgaris, and histologic sections will reveal suppurative folliculitis and superficial perifolliculitis [174]. Incidence of this adverse reaction is lower during lapatinib treatment compared to other ErbB1 inhibitors. About half of patients exposed to lapatinib experience skin toxicity in the first 2 weeks of treatment. However, most are of low grade and resolve spontaneously, and they almost never require interventions, dose reductions, or discontinuation.

Management depends on the type of lesions (pustular vs papular) and extent of distribution. Therapy should be discontinued if more than 50% of body surface is affected. An algorithm for management (Fig. 2.3) has been developed [156, 175]. There is no clear evidence that the occurrence and severity of rash associated with agents used in breast cancer are correlated with tumor response or disease outcome as it is suggested with other anti-EGFR molecules such as cetuximab, erlotinib, and gefitinib [176, 177]. However, early development of rash identified patients who derived superior benefit from lapatinib-based therapy in the NeoALTTO and

ALTTO phase III clinical trials that tested dual blockade with lapatinib and trastuzumab in the neoadjuvant and adjuvant settings, respectively [178, 179].

Further details on skin toxicity are dealt with elsewhere in this book.

2.4.8 Interstitial Pneumonitis

TKI-induced interstitial pneumonitis is a very rare adverse event that can be potentially fatal. It was described with the first approved tyrosine kinase inhibitor imatinib [180]. The majority of cases were described later on with anti-EGFR tyrosine kinase inhibitors mostly used in non-small-cell lung cancer, namely, erlotinib [181, 182] and gefitinib [183], as well as with mTOR inhibitors such as everolimus. Few cases were fatal [183], while the majority recovered with treatment interruption and corticosteroids [184]. Rechallenge is possible [183]. The mechanism involved in TKI-induced interstitial lung disease is unknown but is believed to be idiosyncratic resembling hypersensitivity pneumonia, bronchiolitis obliterans, or eosinophilic pneumonia [185]. Diagnosis is one of exclusion because symptoms mimic congestive heart failure, infection, and lymphangitic carcinomatosis.

Until the use of everolimus in metastatic ER-positive breast cancer, this complication was very rarely described with TKIs used in the treatment of breast cancer. The best description comes from the expanded access program of lapatinib with 0.2% of patients (7/4283) developing pulmonary events: three patients experienced pneumonitis, two interstitial lung disease, and two lung infiltration [186]. Incidence of lapatinib-related interstitial pneumonitis is 0.3% (36/12,795) in the overall lapatinib program [186]. All cases were reversible. Other studies with lapatinib and neratinib report mainly episodes of dyspnea but not interstitial lung disease specifically. Pneumonitis was also reported in 1.1% of patients treated with T-DM1 [171].

Noninfectious pneumonitis associated with mTOR inhibitors needs special attention because of its higher prevalence in a large population (hormone receptor-positive metastatic breast cancer). Its pathogenesis is still unclear and could be related to a cell-mediated autoimmune response after exposure of cryptic antigens or T-cell-mediated delayed-type hypersensitivity. It has also been speculated that mTOR inhibitors may exert part of their action by limiting the destructive remodelling of lung structure. Fortunately, grade 3 and 4 cases remain rare (3% grade 3), and proactive diagnosis as well as treatment following an algorithm (Fig. 2.4) mitigates the risks of serious complications [187].

2.4.9 Hematological Toxicity

Hematological toxicities are not common adverse events of targeted agents. However, neutropenia if the most frequent adverse event described with the use of CDK 4–6 inhibitors such as palbociclib. Fortunately, febrile neutropenia is almost never described as a complication of these transient neutropenic episodes [136, 137].

Thrombocytopenia is another hematological adverse event described with targeted agents for breast cancer. While incidence is <20% with everolimus and palbociclib [135–137], T-DM1 is associated with an incidence rate as high as 32%. T-DM1-associated thrombocytopenia was not fully reversible in all patients and was associated with grade 3 or 4 bleeding in 2% of patients [171].

2.5 Bone-Modifying Agents

Breast cancer shows a high predilection to metastasize to the skeletal system causing multiple morbid events such as pain, hypercalcemia, and fractures, which decrease quality of life.

Bisphosphonates are established therapies for preventing skeletal-related events (SREs) from bone metastases. As a result they are very often prescribed as supportive therapy in advanced breast cancer. Their use is expected to reach the adjuvant setting soon, given the recent demonstration of the ability of zoledronic acid to reduce breast cancer relapses in a low-estrogen environment—e.g., in young women on a LHRH agonist combined with either tamoxifen or anastrozole in postmenopausal women older than 55 years on adjuvant endocrine therapy [107, 188].

Denosumab is a fully human monoclonal antibody that specifically binds human receptor activator of nuclear factor k B ligand (RANKL). RANKL plays a stimulating role in osteoclast activity, thus promoting tumor cell proliferation, metastasis, and survival. By disrupting this activity, denosumab reduces bone resorption, tumor-induced bone destruction, and SREs [189]. In this indication, denosumab is administered subcutaneously every 4 weeks and proved superior to zoledronic acid in delaying or preventing SREs in patients with bone metastases from breast cancer [190]. In postmenopausal patients with breast cancer receiving aromatase inhibitors, adjuvant denosumab reduced the risk of clinical fractures as well as the risk of disease recurrence without added toxicity [109].

Bisphosphonates and RANKL monoclonal antibodies have common toxicities with different incidences, which are reviewed in detail in Chap. 17 of this book.

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Lung Cancer

3

Solange Peters and Stefan Zimmermann

Abstract

Systemic therapy of lung cancer relies on an accurate staging of the disease, identification of key predictive tumor-related biomarkers, but also on careful evaluation of patient characteristics, including capability of tolerating each specific treatment strategy as well as patient's preferences. Therefore, a solid knowledge on all intervention-related adverse events and drug toxicities is essential for an optimal decision-making process.

The majority of lung cancer patients are diagnosed at an advanced, metastatic, stage of the disease, correlated with a dismal prognosis. Systemic palliative therapy remains the mainstay.

This chapter describes the standard drug options and their respective toxicities. Side effects of more complex multimodality treatments of early non-small cell lung cancer (NSCLC) as well as small-cell lung cancer (SCLC), usually using the same cytotoxic agents, jointly with surgery and radiotherapy, are discussed in the second part of this chapter.

Keywords

Non-small cell lung cancer · Small-cell lung cancer · Side effects · Tyrosine kinase inhibitor (TKI) · Platinum doublets · Combined modalities

This is an updated version of the chapter contributed by Stefan Zimmerman, Alessandra Curioni Fontecedro, Rolf A. Stahel, and Solange Peters for book *Side Effects of Medical Cancer Therapy* in 2013. The updates in this chapter were solely done by Solange Peters and Stefan Zimmerman.

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M. A. Dicato, E. Van Cutsem (eds.), *Side Effects of Medical Cancer Therapy*,
https://doi.org/10.1007/978-3-319-70253-7_3

3.1 Non-small Cell Lung Cancer

Lung cancer is the leading cause of human cancer deaths worldwide. Due to the high fatality rate, both incidence and mortality rates reflect the evolution of the smoking epidemic. Whereas incidence has reached a peak in most developed countries in men, only a few countries where prevention policies are most advanced are characterized by a decline in women [1].

Most patients with NSCLC present at an advanced stage of the disease and are symptomatic at the time of diagnosis, with a related poor prognosis and no curative option. For earlier stage I and II disease (cT1a cN0 to cT2c cN1, according to the eighth edition of the TNM staging system), upfront surgery, followed by adjuvant chemotherapy for stage II and selected stage IB patients [2], offers the best chances for long-term survival. In locally advanced, unresectable stage, chemoradiotherapy is recommended, delivered as concurrent (preferred) or sequential manner. In stage IV, systemic palliative treatment is recommended, including cytotoxic chemotherapy, immune-checkpoint inhibitors, and a series of targeted agents in selected molecularly defined subsets of NSCLC patients [3].

3.1.1 Systemic Therapy in Advanced NSCLC

Decisions regarding systemic therapy for advanced NSCLC have traditionally been based on performance status of the patients, comorbidities, and expected toxicity profile. While this still holds true, recent developments introduced further decision factors influencing the choice of therapy, namely, histology (squamous versus non-squamous), the presence of a driver genetic alteration, and the level of PD-L1 (programmed death ligand 1) expression, as well as patients' preference—particularly regarding maintenance strategies and late line of treatment.

3.1.1.1 First-Line Systemic Therapy for Advanced NSCLC

Non-squamous NSCLC

Then identification of genetic alterations driving the malignant phenotype in non-squamous NSCLC offers the opportunity for the use of targeted therapies, making molecular analysis mandatory before treatment selection. Two of these alterations, *EGFR* (epidermal growth factor receptor) mutations and *ALK* (anaplastic lymphoma kinase) rearrangements, determine first-line targeted treatment [3]. Sensitizing *EGFR* mutations predict response to EGFR TKIs (tyrosine kinase inhibitors) gefitinib, erlotinib, afatinib, or dacomitinib, whose use in the first-line setting results in improved response rate, PFS (progression-free survival), and superior quality of life compared with systemic chemotherapy [4]. *ALK* gene rearrangement, identified by FISH (fluorescent in situ hybridization), RT-PCR, or IHC (immunohistochemistry), predicts response to ALK TKIs crizotinib, ceritinib and alectinib, brigatinib, and lorlatinib [5, 6]. *ROS1* gene rearrangement, identified by FISH, RT-PCR, or IHC, predicts response to crizotinib [7].

In the absence of *EGFR* mutation or *ALK* or *ROS1* rearrangement, chemotherapy with platinum-based doublets is preferred [8]. For patients with high level of PD-L1 expression (at least 50% of tumor cell staining), anti-PD-1 immune-checkpoint inhibitor monotherapy pembrolizumab is a more effective option [9].

Overall, a benefit of chemotherapy, in terms of overall survival and quality of life, is observed irrespective of age, histology, and sex, in PS 0-1 and selected PS2 patients [10]. The expected toxicity profile is a major decision factor contributing to the choice of regimen. Aside from tolerability issues, minor efficacy differences between agents or combinations deserve mention. Cisplatin-based combinations show higher response rates than carboplatin-based combinations and possibly longer survival [11]. Pemetrexed-based combinations, particularly in combination with cisplatin, demonstrate a modest survival advantage over docetaxel- or gemcitabine-based combinations [12, 13]. The addition of bevacizumab to carboplatin/paclitaxel improves response rate and overall survival compared with chemotherapy alone [14, 15]. Continuation maintenance therapy with pemetrexed improves PFS and OS [16, 17].

Squamous Cell Carcinoma

As for non-squamous non-small cell lung cancer, pembrolizumab is the standard of care for patients with tumors demonstrating a high level of PD-L1 expression (at least 50% tumor cell staining) [9]. For all others, the combination of a platinum-based regimen with gemcitabine can be considered as a first choice, but other doublets appear similarly effective [10, 18]. The addition of necitumumab, a monoclonal antibody targeting EGFR, to cisplatin and gemcitabine improves OS. This benefit has been restrospectively shown to be restricted to squamous cell lung cancer expressing EGFR [19, 20].

3.1.1.2 Second-Line and Later-Line Systemic Therapy of EGFR- and ALK-Negative Advanced Non-squamous NSCLC

Immune-checkpoint inhibitors targeting the PD-1/PD-L1 axis nivolumab, pembrolizumab, and atezolizumab lead to a significant prolongation of OS compared with docetaxel monotherapy [21, 22]. In later lines of therapy, or in patients ineligible for immune-checkpoint inhibitors, cytotoxic chemotherapy with docetaxel [23] and pemetrexed [24] are commonly used. Erlotinib is an option for patients not eligible for cytotoxic chemotherapy [25] but is inferior to docetaxel in terms of PFS [26]. The addition of antiangiogenic agents ramucirumab [27] or nintedanib [28] to docetaxel improves OS compared with docetaxel alone.

3.1.1.3 Second-Line and Later-Line Systemic Therapy of Advanced Squamous NSCLC

Similarly, nivolumab, pembrolizumab, and atezolizumab lead to a significant prolongation of OS compared with docetaxel monotherapy [22, 29]. In later lines of therapy, or in patients ineligible for immune-checkpoint inhibitors, cytotoxic chemotherapy with docetaxel [23] is commonly used. Erlotinib is an option for patients not eligible for cytotoxic chemotherapy [25] but is inferior to docetaxel in terms of

PFS [26]. Afatinib is another option, having demonstrated improved PFS and OS compared with erlotinib in this setting [30]. The addition of the antiangiogenic anti-VEGFR monoclonal antibody ramucirumab [27] to docetaxel improves OS compared with docetaxel alone.

3.1.1.4 Second-Line and Later-Line Systemic Therapy of EGFR- and ALK-Positive Advanced Non-squamous NSCLC

Most patients treated with a first- or second-generation EGFR TKI will progress within 9–12 months after initiation of therapy and undergo tumor rebiopsy or liquid biopsy [31] for molecular analysis. The most common mechanism of acquired resistance is the acquisition of the T790M mutation in the exon 20 of the EGFR gene, in half of the patients. Consequently, third-generation EGFR TKI osimertinib is the first choice of therapy [32]. A platinum doublet chemotherapy remains the standard of care for cases where the T790M is not detected.

Similarly, most patients treated with ALK TKI crizotinib in first line experience disease progression within 12 months after initiation of therapy. Second-generation inhibitors alectinib [33], ceritinib [34], and brigatinib [35] are current standard options upon progression and furthermore exhibit higher intracranial activity. New ALK inhibitors with a broader range of activity against mutated ALK genes are in development.

3.1.1.5 Palliative Radiotherapy

Palliative radiotherapy might be required to treat painful metastasis (bone, skin, soft tissue) and local complications (e.g., CNS or spinal cord compression) or related to the primary tumor (hemoptysis, vena cava compression, atelectasis due to bronchial obstruction). Usually, at the ear of new radiotherapy delivery techniques, the limited fields limit toxicity attributable to this strategy, which consists mainly of local inflammation-related symptoms and fatigue. A rare side effect is the radiation recall syndrome (RRS), an inflammatory skin reaction that occurs in a previously irradiated body part following drug administration. This phenomenon may occur from days to years following exposure to ionizing radiation.

3.1.1.6 Side Effects of Agents Used for the Systemic Treatment of Advanced NSCLC

Clinical Side Effects of Tyrosine Kinase Inhibitors

EGFR TKIs

First-generation EGFR TKIs erlotinib and gefitinib and the second-generation EGFR TKIs afatinib and dacomitinib prescribed in the first-line setting achieve time to treatment failure times of up to 14.7 months [36, 37]. Due to the prolonged drug exposure, quality of life may be negatively impacted even by low-grade side effects. Overall, the most common are on-target effects, due to inhibition of wild-type EGFR, and include cutaneous and gastrointestinal toxicities. High-grade (grade $\geq$3) adverse events observed in more than 5% of patients include rash (14.6–16.2%) [38, 39],

diarrhea (5.4–14.4%), and stomatitis/mucositis (5.4%) for afatinib [38, 39], and rash (2.3–29.3%), diarrhea (1–8%), and fatigue (2.3–8%) for gefitinib and erlotinib [40–46]. Grade 1–2 dermatologic side effects have been reported in more than 80% of patients and include skin xerosis, pruritus, and acneiform rash. Prophylactic treatment with oral tetracyclines is effective. Topical corticosteroids are used as therapy for grade 1–2 rashes, while systemic corticoids, albeit not evaluated in randomized trials, or low-dose tretinoin [47] is recommended in case of grade ≥3 rashes resistant to oral tetracyclines. Other typical dermatologic side effects include hair changes (as trichomegaly) and paronychia, sometimes progressing up to pyogenic granuloma-like lesions. The most common gastrointestinal side effects of TKIs are diarrhea, described in up to 90% of patients and commonly treated with loperamide, as well as nausea, decreased appetite, and stomatitis. Fatigue has been reported in 5–15% of patients.

Infrequent but potentially fatal complications include an acute interstitial lung disease (ILD) and acute hepatitis [48]. In the only larger head-to-head trial comparing currently used TKIs, afatinib caused more frequent and more severe skin and gastrointestinal toxicity than gefitinib, while gefitinib was associated with more frequent liver enzyme elevation [36]. It is worth noting that all randomized trials that measured quality of life reported a beneficial effect of the TKI compared with cytotoxic chemotherapy.

The third-generation EGFR mutation-specific TKI osimertinib, significantly sparing EGFR WT inhibition, is associated with significantly lower rates of dermatologic and gastrointestinal toxicity. These adverse events proved not to be dose-limiting in the majority of patients. However, its use is limited to EGFR TKI T790M-positive resistant NSCLC pending first-line trial results [32].

ALK TKIs

First-generation ALK TKI crizotinib achieves a median duration of treatment of 10.9 months [5], while second-generation ALK TKIs alectinib and ceritinib achieve median PFS times of more than 16 months in crizotinib-naïve patients [6, 34]. In this context, low-grade side effects will impact quality of life. Frequent high-grade (grade ≥3) adverse events observed with crizotinib include elevated transaminases (14%) and neutropenia (11%). Frequent adverse events (any grade) include vision disorder (71%), diarrhea (61%), edema (49%), vomiting (46%), constipation (43%), elevated aminotransferases (36%), and fatigue (29%). Severe life-threatening fatal pneumonitis has been reported in 1–4% of patients. In men, crizotinib leads to a rapid onset of hypogonadism, sometimes mandating testosterone replacement [49]. Sinus bradycardia and QTc prolongation have been observed.

Second-generation TKIs ceritinib and alectinib have slightly different toxicity profiles, with marked gastrointestinal toxicity induced by ceritinib: all grade diarrhea 85.5%, nausea 77.4%, vomiting 71.8%, and decreased appetite 53.2% [50]. In two large trials comparing two ALK TKIs, alectinib confirmed its favorable toxicity, with 26.2–41% grade ≥3 adverse events compared with 50–51.9% in the crizotinib group, and a marked advantage in all common adverse events: all grade diarrhea 8.7–12 vs 45–73.1%, nausea 10.7–14 vs 48–74%, vomiting 5.8–7 vs 38–57.7%, decreased appetite 1 vs 20.2%, and visual disturbance 1 vs 54.8% [51, 52].

Clinical Side Effects of Antiangiogenic Agents

Bevacizumab

Bevacizumab and other VEGF inhibitors are associated with class side effects related to their mechanism of action [53]. High-grade (grade 3 or higher) adverse events are nonetheless relatively rare and include thromboembolism (8%), hypertension (6%), bleeding (4%), proteinuria (nephrotic range, 3%), and pulmonary hemorrhage (1%). The most common treatment-related serious adverse events are pulmonary embolism (1%) and deep vein thrombosis (1%). Treatment-related mortality occurred in 3% of patients. Bleeding is usually low-grade and leads to permanent discontinuation after 8% of events. Of note, due to a high rate of severe pulmonary hemorrhage and trachea-esophageal fistulas, bevacizumab should not be used concomitantly with thoracic radiotherapy. The same adverse events contraindicate its use for the therapy of squamous cell lung cancer. The risk of intracranial bleeding in patients with untreated, pretreated, or occult brain metastases is not increased [54]. Other class side effects include delayed wound healing, fatigue, and more rarely posterior reversible encephalopathy syndrome [55].

Nintedanib

The addition of nintedanib to docetaxel markedly increases the incidence of diarrhea (all grade 42.3 versus 21.8% for docetaxel alone, grade ≥3 6.6 versus 2.6%), decreases appetite (all grades 22.2 versus 9.3%, grade ≥3 very rare), and vomiting (all grades 16.9 versus 9.3%, grade ≥3 very rare). Docetaxel dose reductions occur more frequently (15.6 versus 11.9%), mainly due to hematological toxicity. Increases in transaminases are frequent but reversible. Hypertension, bleeding, and gastrointestinal perforations are not increased by the addition of nintedanib. Adverse events leading to permanent discontinuation of therapy seem not to occur more frequently with the combination [28].

Ramucirumab

When administered in combination with docetaxel, ramucirumab led to more frequent dose adjustments than docetaxel alone (33 versus 23%). Grade 3 or higher adverse events include febrile neutropenia (16 versus 10%). Consistent with the known class effects of antiangiogenic agents, ramucirumab led to more bleeding or hemorrhage events (29 versus 15%), with no increase in grade 3 or 4 bleeding. Rates of hemoptysis and pulmonary hemorrhage were not increased. Other grade 3 or worse adverse events were rare: fatigue (14 versus 10%) and hypertension (6 versus 2%) [27].

Clinical Side Effects of Chemotherapy

Cisplatin

The most common side effects of cisplatin include fatigue, nausea and vomiting, hematological toxicity, neurotoxicity, nephrotoxicity, and ototoxicity. It remains one of the most emetogenic agents, and prophylactic therapy with a neurokinin 1

antagonist, a 5HT3 antagonist, and corticosteroids is recommended [56]. Myelosuppression is heavily dependent on the companion drug used in common doublet therapies. Neurotoxicity in the form of peripheral polyneuropathy is a dose-limiting side effect, whose incidence and severity are strongly correlated with the total cumulated dose. Hypopallesthesia, hypoesthesia, paresthesias, and autonomic dysregulation may be observed.

Ototoxicity characterized by a dose-dependent sensorineural hearing loss affecting the high frequencies, accompanied by tinnitus, is also often dose-limiting. Due to the bilateral and irreversible nature of this side effect, early detection and early introduction of alternative strategies are mandatory. Nephrotoxicity is a dose-limiting side effect and presents predominantly with acute and chronic renal impairment, which is worsened by prolonged drug exposure, high plasmatic concentrations, preexisting renal disease, and concomitant nephrotoxic drugs. Electrolyte disturbances are frequent, in the form of hypomagnesemia, up to Fanconi-like syndromes.

Carboplatin

Carboplatin was developed to provide a less toxic, more convenient alternative to cisplatin. However, hematologic toxicity is more pronounced than with cisplatin, including severe neutropenia, anemia, and thrombocytopenia [57]. Ototoxicity, neurotoxicity, and renal toxicity occur less frequently with carboplatin compared to cisplatin, but electrolyte disorders can occur in up to 5% of patients. Nausea or vomiting are largely less intense than with cisplatin; the combination of a neurokinin 1 receptor antagonist and an anti-5HT3 palonosetron plus dexamethasone prophylaxis is generally recommended [56]. Of note is the occurrence of infusion reactions reported in up to 15% of patients; these develop more often in patients who have been extensively treated with this medication [58]. Recurrence of such reactions at readministration of carboplatin can be successfully prevented with desensitization procedures.

Pemetrexed [12, 16, 24]

Pemetrexed is generally part of the first-line treatment for adenocarcinoma in combination with a platinum agent and used in monotherapy as continuation maintenance therapy. The most common side effect of pemetrexed is myelotoxicity. The administration of vitamin B12 concurrent with folate acid has reduced its hematotoxicity to a very moderate level, with grade 3 and 4 neutropenia occurring in only about 15% of patients. Nausea and vomiting have been reported in less than 5% of patients. A common grade 1–2 side effect is constipation.

Gemcitabine [59, 60]

Toxicity of gemcitabine is generally mild and reversible after discontinuation of medication. The most common side effects are flu-like symptoms in about 50% of patients, with fever or arthralgia. Edema is also often observed and does not correlate with renal or cardiac dysfunction [61]. Grade 3–4 myelosuppression occurs infrequently, including anemia (5%), thrombocytopenia (1%), leukopenia (7%), and neutropenia (22%), rarely resulting in neutropenia-related infection. Grade 3–4 liver toxicity can be detected in up to 10% of patients. Nausea and vomiting often

occur but are of low grade and can be prevented with a single antiemetic agent such as dexamethasone, a 5-HT_3 receptor antagonist, or a dopamine receptor antagonist. Severe lung toxicity has been described in the range of 0.1–1.4% [62, 63]; gemcitabine can rarely cause drug-induced thrombotic microangiopathy [64].

Docetaxel [23, 65]
The most common side effects of docetaxel are myelotoxicity and fatigue. The rate of grade 3 or 4 neutropenia due to docetaxel varies from 40 to 60% (according to dosage), and the risk of neutropenic fever exceeds 10%. Nonhematologic toxicities include alopecia, nail changes, mild nausea and vomiting, and allergic manifestations such as skin rash and pruritus. Cumulative fluid retention, sometimes dose-limiting, can be delayed with pretreatment with corticosteroids [66]. Hypersensitivity reactions to docetaxel are rare.

Clinical Side Effects of Immunotherapy

Nivolumab, Pembrolizumab, Atezolizumab, and Durvalumab
Monotherapy with anti-PD1/PD-L1 monoclonal antibodies is well tolerated [21, 22, 29, 67]. The most common treatment-related grade 3 adverse events are fatigue (1%) and nausea (1%), and the most common severe treatment-related adverse event is pneumonitis (1–4%). Overall, grade 3 or 4 adverse events do not exceed 15%. The most common adverse events of any grade are fatigue (16%), nausea (12%), decreased appetite (10%), rash (9%), diarrhea (8%), hypothyroidism (7%), and increased liver transaminases (3%). Moderately severe immune-related adverse events are commonly managed with temporary treatment interruption until resolution to grade 1 or less and sometimes with corticosteroids in the absence of resolution within a week. For more severe immune-related adverse events (grade 3 or more), permanent discontinuation is recommended, and corticosteroids (minimum of 1 mg/kg prednisone-equivalent) should be administered. In the absence of improvement after 48 h, infliximab or other immunomodulatory drugs should be considered. Corticosteroids are subsequently tapered over at least 1 month.

Nivolumab leads to significant improvements in health status from baseline and slower deterioration of quality of life, as well as a meaningful improvement in mean symptom burden in patients remaining on treatment [68, 69].

Patients with preexisting autoimmune disorders have been excluded from clinical trials of immune-checkpoint inhibitors in lung cancer. Retrospective studies of nivolumab or pembrolizumab in such patients suggest the existence of autoimmune flare requiring immunosuppression, mostly mild, with most patients being able to continue therapy [70, see Chap. 12].

3.1.2 Systemic Therapy in Locally Advanced NSCLC

Locally advanced NSCLC is treated with multimodality approaches, including chemotherapy, radiotherapy, as well as surgery in selected cases, commonly stage IIIA

(N2). Unresectable disease such as stage IIIB NSCLC is approached with chemoradiotherapy, preferentially delivered in a concurrent fashion [71]. The optimal systemic therapy delivered with radiotherapy is undefined; cisplatin-based chemotherapy doublets have yielded the best results in randomized trials [72], with side effects in line with their profile observed during therapy of advanced disease. While neither induction chemotherapy [73], consolidation chemotherapy [74], nor consolidation targeted therapy [75] has demonstrated an improvement in overall survival, durvalumab consolidation is emerging as new standard of care after concurrent definitive chemoradiotherapy [76].

3.1.3 Treatment of Early NSCLC

3.1.3.1 Surgery

Lobectomy and systematic lymph node dissection are considered standard therapy for early (stage I and II) NSCLC. Sublobar resection by means of an anatomical segmentectomy may lead to equivalent survival rates among patients with stage I NSCLC less than 1 cm in size and is associated with fewer complications and better postoperative lung function [77, 78]. A thirty-day mortality rate after lobectomy is expected to be lower than 2% in high-volume hospitals [79]. Pretreatment pulmonary function tests are well-known predictors of surgical risk [80–82].

Anatomical resections are currently performed according to the Bolliger and Miller algorithms that are based on forced expired volume in 1 s (FEV1) and lung carbon monoxide diffusion capacity (DLCO). The percentage of predicted FEV1 and DLCO values were shown to correlate with patient outcome (hospital and overall mortality) in patients undergoing resections. Postoperative complications and mortality were also shown to be correlated, even with a large variability, to hospital volume and surgeon skills [83]. Pneumonectomy is seldom indicated in stage I and II NSCLC, but it is associated with a higher operative mortality rate, especially for right pneumonectomy [84].

Minimally invasive video-assisted lobectomy was shown to be equivalent to open lobectomy in terms of locoregional recurrences. Data suggest a reduced systemic recurrence rate and an improved 5-year mortality rate, but since most studies were not randomized, the effect of case selection is difficult to ascertain, even if highly probable [85]. Complete mediastinal lymphadenectomy adds little morbidity to a pulmonary resection for lung cancer and possesses a prognostic impact [86, 87].

A consistent proportion of patients undergoing lung resection exhibit an important postoperative worsening in their quality of life: 28% in the physical component summary and 15% in the mental component summary. Patients with a better preoperative physical functioning and those with worse mental health scores were those at higher risk of a relevant physical deterioration. Patients with a lower predicted postoperative forced expiratory volume in 1 s (ppoFEV1) and higher preoperative scores of social functioning and mental health were those at higher risk of a relevant emotional deterioration. Compared with the general population, nearly half of the patients displayed a depressed physical and emotional status 3 months after surgery

[88]. The extent of resection, age, and adjuvant therapy was associated with a clinically relevant decline in the physical aspect of health-related quality of life 6 months after surgery [89].

3.1.3.2 Adjuvant Chemotherapy

Despite optimum surgical management, the 5-year survival rate of resected NSCLC ranges from 25 to 75% according to pathologic stage. A large meta-analysis by the NSCLC Collaborative Group suggests an absolute improvement in 5-year survival with platinum-based chemotherapy of 5% [2–5, 8, 9] for stage IB (from 55 to 60%), 5% [3–5, 8–10] for stage II (from 40 to 45%), and 5% [3–5, 8–10] for stage III disease (from 30 to 35%) [2, 90]. Another large meta-analysis showed a detrimental effect of adjuvant chemotherapy in stage IA NSCLC [91]. The most commonly used regimens are cisplatin in combination with vinorelbine or etoposide. Cisplatin and vinorelbine adjuvant chemotherapy is associated with frequent hematologic toxic effects, including high-grade neutropenia in 85% of patients. Common nonhematologic effects include asthenia and nausea or vomiting. There are approximately 2% treatment-related deaths, mainly from infection [92]. Overall, compliance and, as a consequence, dose intensity and total dose of adjuvant chemotherapy are disappointing. Altogether, 59% of patients receive at least 240 mg/m^2 of cisplatin, this parameter being potentially more important than the choice of the second compound [91, 93]. Fourteen percent of patients received only one cycle and 10% only two cycles, mainly because of patient refusal (35%), toxicity (34%), and early death or progression (9%). The median delay between surgery and the start of chemotherapy was 39 days (>60 days in 7% of patients).

The beneficial effect of adjuvant chemotherapy on recurrences does not decrease with longer follow-up, and there is no increase in the number of secondary malignancies. However, the maintained beneficial effect of preventing lung cancer deaths contrasts with a probable chemotherapy-induced increase in non-lung cancer mortality after 5 years that can decrease but not nullify the beneficial effect of adjuvant therapy [94]. Statistically significant causes of non-cancer deaths after cisplatin-based chemotherapy in the non-lung cancer setting were infections and cardiovascular and respiratory diseases [95].

3.1.3.3 Postoperative Radiotherapy

Postoperative radiotherapy (PORT) should be delivered in case of incomplete resection (ref ESMO guidelines).

However, PORT has a detrimental effect on survival in patients with early stages I and II [96, 97]. This is in contrast with N2 disease, where the PORT-induced morbidity might be outweighed by the presence of residual microscopic disease. With the limitation related to the availability of retrospective data only, where confounding factors in patient selection may have biased this interpretation, radiotherapy-related toxicity might be involved in the negative impact of PORT, which is recommended to date after radical resection.

3.2 Small-Cell Lung Cancer

Small-cell lung cancer (SCLC) accounts for approximately 15% of primary lung carcinoma. It is invariably associated with tobacco exposure and is characterized by rapid tumor doubling time and early development of metastases. Less than 10% of patients are asymptomatic at diagnosis. Of all histologic subtypes of lung cancer, SCLC is the most sensitive to chemotherapy and radiotherapy, but prognosis remains dismal. Staging of SCLC is made according to the 7th TNM classification and according to a two-stage system developed by the Veteran's Administration Lung Cancer Study Group, dividing patients into limited (stages IA to IIIB) or extensive (stage IV) stage disease. Limited disease is thus defined as disease confined to one hemithorax (i.e., disease that can be included in a "tolerable" radiation field). Approximately one-third of patients present with clinical definition of "limited disease," but most of these patients already present with subclinical metastatic disease. The current standard of care has not changed in the last two decades, with most advances being restricted to improved radiation approaches. The standard first-line chemotherapy regimen in Caucasian patients remains cisplatin or carboplatin plus etoposide in the treatment of limited stage and extensive stage disease. Radiation therapy is administered to those patients with limited stage small-cell lung cancer whose cancer is confined to the chest in a single tolerable radiation field: data support initiation of radiation during cycle one or two and use of hyperfractionated radiation therapy.

3.2.1 Limited Disease

The standard treatment for limited disease SCLC is combined-modality therapy consisting of thoracic radiotherapy and systemic chemotherapy. Two meta-analyses have shown an improvement of survival in patients who received chest irradiation in addition to chemotherapy compared to those receiving chemotherapy alone [98, 99], with an aim for long-term remission in only a small fraction (15–25%) of these patients. The optimal timing of radiotherapy, either concurrent or sequential, remains unsettled, with compelling evidence that early radiotherapy concurrent with platinum-based chemotherapy is superior to sequential radiotherapy [100, 101].

The addition of concurrent radiotherapy to chemotherapy results in increased myelosuppression than that observed with sequential treatment, with 88 versus 54% high-grade leukopenia, respectively [102]. Nonhematologic toxicities are similar, with a trend toward more infections and esophagitis. The incidence of severe pneumonitis is not significantly different between early and late chest radiotherapy, ranging between 2 and 17% in studies with platinum-based chemotherapy. Treatment of choice consists of oral corticosteroids. The fractionation of radiotherapy might also play a role, with one trial showing a survival advantage with twice-daily versus once-daily radiotherapy, albeit with unequal biologic effective dose [103].

Hyperfractionated radiotherapy resulted in significantly more esophagitis than once-daily fractionation and may occasionally mandate tube feeding.

3.2.2 Extensive Disease

Chemotherapy is the mainstay of treatment for patients with SCLC because of its proclivity for early dissemination. Standard chemotherapy in Caucasian patients consists of cisplatin and etoposide, having been proven equivalent and more tolerable than older regimens such as cyclophosphamide, doxorubicin, and vincristine [104]. Toxicity is mainly hematologic, especially neutropenia, 30–40% being grade 3–4. Granulocytopenia can be effectively prevented with recombinant granulocyte colony-stimulating factor (G-CSF). Nonhematologic toxicity is essentially gastrointestinal, with little high-grade nausea or vomiting. All other clinically significant nonhematologic toxicities, excluding alopecia, were present in fewer than 4% of patients. Thoracic radiation therapy is now being applied to responding patients with extensive stage SCLC, after a phase III trial showed considerable reduction in intrathoracic recurrence and in 2-year overall survival [105]. No severe toxic effects were recorded, and the most common grade 3 or higher toxic effects were fatigue (11 versus 9%) and dyspnea (3 versus 4%).

3.2.3 Prophylactic Cranial Irradiation

Patients responding to first-line treatment, irrespective of stage, are usually offered prophylactic cranial irradiation (PCI), which has been shown to markedly reduce the cumulative incidence of brain metastases both in patients with limited or extensive stage disease, as well as increase survival in limited stage SCLC [106–108]. The impact of PCI on survival in patients with extensive stage SCLC who respond to chemotherapy is uncertain [109].

PCI results in significantly more early and late (at 6 weeks and 3 months, respectively) fatigue, early and late appetite loss, nausea and vomiting, and early and late leg weakness.

Long-term toxicities and particularly cognitive deficits are difficult to assess, and trials yield conflicting results. A higher total dose of 36 Gy resulted in significant deterioration in neurologic function (defined as a decrease in any neuropsychological test) and increased chronic neurotoxicity (defined as deterioration in at least one neurocognitive test without documentation of brain metastases) as compared to a lower total dose of 25 Gy—without any benefit in terms of mortality and a higher incidence of subsequent brain metastases [110]. Other trials reported a negative impact on early quality of life and a limited negative impact on functioning scales of PCI, with a maximum difference in role, emotional, and cognitive functioning between 6 weeks and 3 months, then decreasing [111]. Memory-sparing strategies, as hippocampal-sparing PCI, are currently under evaluation.

3.2.4 Second-Line Therapy

Relapsing patients are offered second-line chemotherapy with the goal of an improvement in survival and preservation of quality of life. Oral and intravenous topotecan are classical compounds in the second-line setting. Oral topotecan extends overall survival even in patients with short (<60 days) treatment-free interval and delays deterioration of quality of life as compared to placebo [112]. Toxicity from oral topotecan is mainly hematologic, with 60% of patients presenting with high-grade neutropenia. The most frequent nonhematologic toxicities are diarrhea and fatigue. There were fewer early deaths (<30 days) and greater likelihood of achieving symptom improvement for all symptoms, including shortness of breath, sleep interference, and fatigue. Beyond this long-standing standard cytotoxic immunotherapy is intensively studied in that setting, with promising early results using dual checkpoint inhibition with the combination of anti-CTLA4 and anti-PD1 antibodies [113].

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4

Gastrointestinal Cancer: Selection of Clinically Relevant Drug-Induced Toxicities Encountered in Gastrointestinal Cancer Treatment

Julie Bogaert, Pieter-Jan Cuyle, and Eric Van Cutsem

Abstract

The chemotherapeutic options have increased dramatically in patients with gastrointestinal cancer and have led to an improved outcome. With this, an in-depth understanding of the side effects of chemotherapy is becoming increasingly important in order to minimize the negative impact of the use of these agents. Chemotherapeutic agents have a long list of potential side effects. In this chapter, we focus specifically on some of the more common and/or more relevant and challenging side effects related to frequently used agents in gastrointestinal cancer. The fluoropyrimidines may cause cardiac toxicity, most frequently angina-like chest pain. The knowledge of the catabolism of fluorouracil has led to the possibility of testing for dihydropyrimidine dehydrogenase (DPD) in order to avoid serious fluorouracil-related toxicity in patients with DPD deficiency. Oxaliplatin-induced neurotoxicity is probably the most important clinical problem associated with the administration of oxaliplatin. With the increasing use of oxaliplatin, hypersensitivity reactions are more frequently reported and become challenging in clinical practice. The introduction of the targeted agents in colorectal cancer led also to specific problems: the anti-VEGF-related side effects, of which arterial thrombosis and gastrointestinal perforation, although relatively rare, are very relevant for the patient, and the anti-EGFR-related side effects, including skin rash, hypomagnesemia, and allergic reactions, are common. Understanding the underlying causes,

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M. A. Dicato, E. Van Cutsem (eds.), *Side Effects of Medical Cancer Therapy*,
https://doi.org/10.1007/978-3-319-70253-7_4

mechanisms, risk factors, and developing treatment guidelines has made these side effects often more acceptable for many patients. However, the side-effect profile always has to be balanced against the activity and benefit of the anticancer agents.

Keywords
Fluorouracil · DPD · Oxaliplatin · Irinotecan · VEGF · EGFR · Bevacizumab Cetuximab · Panitumumab

4.1 Fluoropyrimidines: Fluorouracil and Capecitabine

Since the late 1950s, fluorouracil (5-FU) has been used as a cytotoxic chemotherapeutic agent to treat various types of solid malignancies originating from breast, esophagus, larynx, and gastrointestinal and genitourinary tracts. Because of its variable gastrointestinal absorption and rapid degradation, 5-FU must be administered intravenously [1]. We have learned to use the most optimal regimens of 5-FU: it has been shown that infusional regimens lead to less adverse events compared to bolus regimens of 5-FU. Capecitabine (Xeloda, Roche Pharmaceuticals, Nutley, NJ, USA), an oral prodrug of 5-FU, shows a favorable toxicity profile and comparable efficacy end points in gastric and colorectal cancer [2]. Capecitabine undergoes a three-step enzymatic conversion to 5-FU that occurs primarily in the liver and tumor cells, thereby achieving high intratumoral drug concentrations.

Adverse events of fluorouracil and its prodrug capecitabine are summarized in Table 4.1. Fluorouracil-related severe adverse events can cause substantial morbidity and also very occasionally death, suggesting an important role for pharmacogenomics in identifying patients at risk for increased toxicity. Fluoropyrimidine-induced cardiotoxicity is relatively infrequent and generally reversible on treatment discontinuation. However, this complication can be life-threatening, and fatal outcome has been described.

Table 4.1 Common side effects of frequently used cytotoxic agents in GI cancer

Fluorouracil (5-FU)	**Capecitabine**
Hematologic	Hematologic
Mucositis/diarrhea	Mucositis/diarrhea
Stomatitis	Hand-foot syndrome
Hand-foot syndrome	Cardiac adverse events
Cardiac adverse events	

Oxaliplatin	**Irinotecan**
Hematologic	Hematologic
Nausea/vomiting	Nausea/vomiting
Neurotoxicity	Mucositis/diarrhea
Infusion reactions	Alopecia

4.1.1 Fluorouracil-Induced Cardiac Toxicity

The incidence of 5-FU-related cardiac toxicity varies broadly throughout the literature but is reported in most studies below 3% [3]. In fact, the real incidence may be even higher, as asymptomatic ischemic electrocardiography (ECG) changes do occur also [4]. This side effect may occasionally be fatal [3]. Angina-like chest pain is the most frequent presenting symptom of cardiac toxicity, and it is reported in up to 89% of patients with cardiac toxicity [3]. Less common symptoms include palpitations and malaise. Clinical pictures of congestive heart failure, cardiogenic shock, cardiac arrest, and sudden death have been reported. ECG findings may include myocardial ischemia, myocardial infarction, and cardiac arrhythmias [5]. Serum cardiac enzyme levels are usually normal, and echocardiography can reveal transient local or, more frequently, global, myocardial hypokinesia compatible with myocardial stunning [3]. Usually no significant coronary atherosclerosis is found when coronary angiography is performed. Most events occur during or within several hours after fluorouracil treatment, since the serum half-life of 5-FU is very short [3]. Symptoms are usually fully reversible shortly after treatment discontinuation.

Pathophysiologic mechanisms involved in fluorouracil-associated cardiotoxicity remain incompletely understood and are probably multifactorial. Based on the characteristic clinical and ECG presentation in the absence of relevant coronary stenosis, this phenomenon is historically attributed to fluorouracil-induced coronary vasospasm [6]. However, other mechanisms have been proposed. Data from animal models and echocardiographic studies suggest a direct toxic effect of 5-FU metabolites on the myocardial cells, resulting in toxic myocarditis and cardiomyopathy [4, 5]. Risk factors for development of fluorouracil-induced cardiotoxicity have not been specified. The impact of preexisting heart disease remains controversial [3]. Previous or current radiation involving the heart may promote cardiac toxicity. The toxic effect of 5-FU/capecitabine on the myocardium is schedule-dependent. Cardiac symptoms occur more frequently with the use of continuous 5-FU infusion, when compared to a short (bolus) administration of 5-FU [5]. Pharmacokinetics of capecitabine are comparable to that of continuous 5-FU infusion, and incidence of cardiotoxicity is reported to be similar to that of 5-FU [7]. The other approved oral fluoropyrimidines, S1 and trifluridine/tipiracil, may also cause similar cardiac adverse events.

Baseline ECG testing before starting a treatment with 5-FU-based chemotherapy could be helpful in future assessment of cardiotoxicity. Baseline echocardiography is recommended for patients with a history of heart disease [3, 4]. Patients in whom cardiotoxicity is suspected should receive cardiac monitoring because of the possible risk of life-threatening heart failure and malignant arrhythmias. Fluorouracil administration should be stopped immediately. Symptomatic treatment with nitrates and/or calcium antagonists is recommended [3]. However, the reported therapeutic efficacy of these drugs is inconsistent, and no prospective trials are available. The risk of relapse when patients are reexposed to 5-FU following previous cardiac incidents is very high, up to 82–100% [3]. Whether the use of prophylactic antianginal medication can reduce the recurrence risk has not been established, but it is often

done in patients with mild symptoms when the continuation of the fluoropyrimidine is advisable. Administration of raltitrexed (Tomudex, TDX, ZD 1694, AstraZeneca, Wilmington, DE, USA) as an alternative for 5-FU, in case of major intolerance, is often suggested [8].

4.1.2 Dihydropyrimidine Dehydrogenase Deficiency

Dihydropyrimidine dehydrogenase (DPD) is the primary rate-controlling enzyme in fluoropyrimidine catabolism. Over the last two decades, the association between DPD-enzyme deficiency and the occurrence of severe fluorouracil-related toxicity has been extensively studied. Patients receiving 5-FU-based chemotherapy may develop severe to life-threatening adverse events, including neutropenia, neutropenic infections, stomatitis, diarrhea, and alopecia, and it is estimated that DPD deficiency accounts for 50–75% of the cases of severe side effects [9].

The human dihydropyrimidine dehydrogenase (DPYD) gene, encoding DPD, is located on chromosome 1p22 and contains 23 exons. Loss-of-function mutations in this DPYD gene lead to a partial or complete lack of capacity to metabolize 5-FU or its prodrugs, explaining the risk of increased toxicity. DPD-enzyme activity is highly variable within the normal population and differs substantially between ethnic subpopulations. The prevalence of partial DPD deficiency (low DPD activity) is estimated to be 3–5% in the overall population [10, 11]. Complete DPD deficiency was first described as an autosomal recessive disorder in pediatric patients with various neurological symptoms [10, 12].

Over 50 genetic variants have been identified in the DPYD gene coding region—however, the majority without functional consequences on enzymatic activity [9, 10]. The most prominent and most studied DPYD variant is a point mutation in the splice site of intron 14 (c.1905 + 1G > A, synonyms IVS14 + 1G > A or DPYD*2A), responsible for up to 29% of reported grade III–V toxicities following fluorouracil administration [13]. Conflicting results were seen in a more recent prospective trial, which concluded that severe toxicities could only be marginally attributed to DPYD gene polymorphism [14]. Furthermore, it is suggested that additional enzymes and polymorphisms in various downstream acting genes may also play a role in 5-FU degradation and toxicity [9]. The pronounced variability in the DPYD coding sequence, together with contradictory results from genetic studies, causes marked difficulties in genotype-phenotype correlations and presents a major limitation to the application of a genotype-based strategy to predict severe fluorouracil toxicity in daily practice [9].

Alternatively, a number of functional screening tests assessing DPD functionality (phenotype-based strategy) have been developed to predict impaired fluorouracil metabolism [9, 10, 15]. Enzymatic activity can be measured ex vivo in peripheral mononuclear blood cells or can be estimated through analysis of the plasma or urine dihydrouracil/uracil (UH2/U) ratio. A noninvasive uracil breath test measuring exhaled $^{13}CO_2$ after ingestion of 2-^{13}C-uracil or administration of an infratherapeutic 5-FU test dose followed by pharmacokinetic analysis is another possibility for

preliminary functional testing. Clinical data implementing systematic pretreatment functional DPD testing and subsequent DPD-based 5-FU dose tailoring are limited. However, these data suggest that this approach is feasible, reducing treatment-related severe toxicities without a loss in treatment efficacy [9, 16].

Anticipating and preventing 5-FU-related severe toxicities has been suggested to be cost-effective, to enhance patient quality of life, and to reduce chemo- or radiotherapy postponement, thus improving patient outcome [9]. The exact relevance of systematic DPD testing and whether genetic or functional testing is more practical and predictive in daily practice are questions that remain to be answered. However, more recently genetic testing is clearly favored. Therefore, routine screening for DPD deficiency is not performed in most institutions. However, if there is a clinical picture of very severe toxicity, especially early on in the treatment of a fluoropyrimidine, DPD testing is indicated and can avoid later life-threatening toxicity.

4.2 Oxaliplatin

Oxaliplatin (Eloxatin, Sanofi-Aventis, Bridgewater, NJ, USA), a third-generation platinum derivative, has been investigated in different types of malignancies and was shown to be particularly efficacious in the treatment of gastrointestinal neoplasms, including esophagogastric, pancreatic, and colorectal cancers [17]. Combinations of oxaliplatin with infusional fluorouracil/leucovorin (FOLFOX) or capecitabine (XELOX) have emerged as important therapeutic options in the adjuvant as well as palliative treatment of colorectal cancer [18]. Oxaliplatin has proved to be an equivalent alternative for cisplatin, with a slightly favorable toxicity profile, especially in terms of renal toxicity in gastric and pancreatic cancer. Common side effects are summarized in Table 4.1. Oxaliplatin-induced neurotoxicity and hypersensitivity infusion reactions are well-recognized dose-limiting toxicities, often encountered in clinical practice, potentially resulting in permanent discontinuation.

4.2.1 Oxaliplatin-Induced Neurotoxicity

Oxaliplatin-induced neurotoxicity (OXIN) is the most frequent clinically relevant adverse event associated with the use of oxaliplatin [18]. It is a cumulative and dose-limiting complication in which symptoms are typically triggered or worsened by exposure to cold. Common terminology criteria for adverse events (CTCAE) are often used for grading and monitoring OXIN. Development of grade ≥2 neuropathy (CTCAE version 4.0) occurs in approximately half of treated patients, and 10–20% of patients develop grade 3 neuropathy [19, 20]. In up to 90% of patients, peripheral neuropathy reverses after oxaliplatin is discontinued—however, sometimes with a long delay. Symptom worsening is reported for up to 8 weeks after the last dose of oxaliplatin, also after surgery, and in some cases neuropathy may persist for several months or even years or may even not be completely reversible.

Two distinct forms of OXIN are recognized: an acute type and a chronic type [17, 18]. Acute sensory and/or motor neurotoxicity occurs during or within 1–2 days after oxaliplatin infusion. It shows a rapid onset and is characterized by paresthesia and dysesthesia affecting the acral segments of both upper and lower limbs; it is clearly exacerbated by cold exposure. The perioral and laryngopharyngeal areas may be involved as well, possibly leading to an acute sensation of respiratory discomfort. Acute motor neuropathy is associated with symptoms of muscular hyperactivity, such as jaw tightness, cramps, and fasciculations, that affect legs, thighs, hands, and jaws, hampering movements. Acute symptoms usually resolve spontaneously within a week but usually relapse with each subsequent administration of oxaliplatin, often with slightly increasing intensity after each course.

Chronic oxaliplatin-associated neuropathy is a dose-limiting chronic sensory neuropathy that involves the extremities, possibly causing functional impairment and even gait ataxia with longer treatment exposure. It becomes worse with increasing cumulative doses of oxaliplatin.

The pathophysiological mechanisms responsible for the development of OXIN remain unclear. In the acute form, oxalate, a metabolic by-product of oxaliplatin, may cause a dysfunction of the neuronal voltage-gated calcium-dependent sodium channels, disrupting intracellular homeostasis and provoking neuronal hyperexcitability [21, 22]. In the chronic form, accumulation of platinum compounds in neurons may lead to neuronal atrophy. Several studies have tried to identify pharmacogenomic markers (single nucleotide polymorphisms or SNPs) predisposing patients to severe neurotoxicity development; however, no such marker has been validated for clinical use to this date [23, 24].

To avoid the occurrence of severe, long-lasting, and invalidating OXIN, gradual dose reductions and delay or discontinuation of oxaliplatin administration are often necessary, without a clear impact on the overall outcome. Indeed, stop-and-go strategies have been developed in metastatic colorectal cancer, mainly as a consequence of this cumulative neuropathy [25, 26]. Several trials have investigated the neuroprotective potency of calcium and magnesium infusions. As oxalate chelators, they are thought to reduce the effect of oxalate on the voltage-gated sodium channel, thereby reducing OXIN severity [27]. Although calcium and magnesium are frequently administered before and after oxaliplatin, the lack of standardization in the use and timing of objective neurotoxicity assessment and the lack of long-term neuropathy data in these studies have often led to different conclusions. Recently, however, a randomized trial could not show the benefit of the administration of calcium and magnesium on the occurrence of neurotoxicity [28]. The neuroprotective efficacy of several pharmacologic agents, such as antidepressants and anticonvulsants, has been studied in a number of trials, which are nicely summarized in a recent review by Weickhart et al. [17]. Venlafaxine has been shown to reduce the incidence of acute and chronic peripheral neuropathy in patients treated with oxaliplatin in a small phase III trial [29]. At the present time, however, no strong evidence is available supporting the systematic use of these agents in the prevention or treatment of oxaliplatin-associated neuropathy. Acute oxaliplatin-induced neuropathy of the

laryngopharyngeal area is often confused with allergic laryngeal angioedema but is usually manageable by prolonging oxaliplatin infusion time to 6 h, without specific antiallergic premedication.

4.2.2 Oxaliplatin-Associated Hypersensitivity Infusion Reactions

Hypersensitivity to chemotherapy is historically defined as an unexpected reaction, with signs and symptoms that are inconsistent with the drug's usual toxicity profile occurring during or immediately following the administration of that drug [30, 31]. Due to the extensive use of oxaliplatin in cancer treatment over the last decade, the drug is increasingly recognized to cause hypersensitivity reactions similar to those seen with earlier generations of platinum-based compounds, at an overall incidence of 10–20% [30–32]. However, severe grade 3–4 reactions are less common, occurring in 1.6% of the patients, and severe anaphylaxis is reported rarely [30, 31]. Symptoms often develop acutely during oxaliplatin infusion or shortly afterward and usually occur within the first 24 h after infusion. Mild hypersensitivity reactions are characterized by skin rash, urticaria, flushing, palmar itching, burning, edema of the face and hands, abdominal cramping and diarrhea, back pain, and pruritus [30]. More severe infusion reactions can present with the development of bronchospasm, tachycardia, hypo- or hypertension, angioedema, seizures, and chest pain. Hypersensitivity events are generally encountered after four to six oxaliplatin administrations [31].

Most infusion reactions seem to be IgE-mediated (type I), but type II hypersensitivity with symptoms of hemolysis and thrombocytopenia or type III allergic reactions with development of chronic urticaria, joint pain, and proteinuria have also been reported [30]. Furthermore, idiosyncratic reactions to oxaliplatin infusion, characterized by chills, fever, abdominal cramps, and chest tightness, have also been described. A recent retrospective study has identified the presence of a younger age, female sex, and the use of oxaliplatin as salvage therapy as potential risk factors for development of oxaliplatin-associated infusion reactions [31]. However, the presence of prior allergies, disease type, and stage or treatment regimen did not seem to be associated with increased hypersensitivity.

When a hypersensitivity infusion reaction is diagnosed, the chemotherapy infusion should be interrupted promptly, followed by infusion of normal saline and administration of oxygen, systemic antihistamines, and corticosteroids. Other supportive measures should be taken as indicated until complete resolution of symptoms. The main dilemma is whether oxaliplatin can be readministered in the future. The decision should be based on the severity of the hypersensitivity reaction, on the patient's general condition, and on the anticipated oncological benefit of oxaliplatin administration. In case of mild and moderate hypersensitivity reactions, reintroduction can be successful by prolonging the infusion time to 4–6 h and the use of premedication with histamine receptor antagonists and corticosteroids [32].

Nevertheless, the risk of recurrence is estimated around 30–40%. When the reaction is relatively severe (grade ≥ 3), all platinum compounds should be excluded from future treatment options. Various desensitization protocols have been successfully implemented for cisplatin and carboplatin; however, oxaliplatin desensitization protocols have only been reported in a very small number of patients [30].

4.3 Vascular Endothelial Growth Factor Inhibition: Bevacizumab, Aflibercept, and Ramucirumab

Neo-angiogenesis is crucial for tumor growth and malignant progression. In the majority of cancers, tumor vessels appear to be abnormal in structure and function, leading to a hostile microenvironment characterized by hypoxia, low pH, and high interstitial fluid pressure [33]. The spread of tumor cells, escaping through these leaky vessels, is facilitated, while, on the other hand, transport and distribution of cytotoxics and oxygen to the tumor seem to be impaired. One of the main angiogenic factors is vascular endothelial growth factor (VEGF). Blockade of VEGF signaling by pharmacologic agents can transiently repair these vascular abnormalities, thus improving oxygenation and lowering interstitial fluid pressure. This process is referred to as vascular normalization [33]. The decrease in interstitial fluid pressure improves cytotoxic drug delivery to the targeted cancer cells. Bevacizumab (Avastin, Genentech, South San Francisco, CA, USA) is a recombinant, humanized monoclonal antibody to VEGF-A, which inhibits binding of VEGF to its receptors, hereby suppressing downstream signaling of the VEGF pathway. Aflibercept (Zaltrap, Sanofi US and EU) is a fusion protein binding to VEGF-A, VEGF-B, and placenta growth factor (PlGF), and ramucirumab (Cyramza, Lilly, USA) is an antibody binding directly to the receptor, VEGFR2. The combination of bevacizumab with standard chemotherapy (irinotecan/5-FU, oxaliplatin/5-FU, or a fluoropyrimidine alone) and of aflibercept or ramucirumab with chemotherapy (irinotecan/5-FU) has been shown to improve the clinical outcome in patients with metastatic colorectal cancer but not in the adjuvant setting [34, 35]. Moreover ramucirumab has activity in the second-line treatment of gastric cancer, either as single agent or in combination with paclitaxel. The clinical toxicities associated with the use of VEGF inhibitors have been well described and are summarized in Table 4.2. The side effects are class-related and are seen with the different anti-VEGF targeting agents: the most important include arterial hypertension, proteinuria, mucosal bleeding, arterial thrombosis (especially in older patients with a history of arterial thrombosis), wound healing complications, and gastrointestinal perforation. Serious adverse events are relatively uncommon, and side effects are generally manageable using standard treatment. Bevacizumab does not increase the typical chemotherapy-induced side effects, such as diarrhea, stomatitis, neutropenia, and neutropenic infections, although other agents interfering with VEGF (aflibercept, VEGF tyrosine kinase inhibitors) have been reported to be associated with a higher incidence of the aforementioned chemotherapy-related side effects.

Table 4.2 Common side effects of frequently used biological agents in GI cancer

EGFR inhibition: cetuximab and panitumumab
Skin toxicity
Hypomagnesemia
Infusion reactions
VEGF inhibition: bevacizumab, aflibercept, ramucirumab
Hypertension
Proteinuria
Delayed wound healing
Gastrointestinal perforation
Bleeding
Arterial thromboembolic events

4.3.1 Bevacizumab-Associated Gastrointestinal Perforation

The occurrence of gastrointestinal (GI) perforation, a potentially life-threatening complication of bevacizumab treatment, has been reported in patients with various types of solid tumors, although it is typically more frequent, for reasons that are unclear, in the management of colorectal and ovarian cancer [36]. In pivotal clinical trials and two community-based observational studies that investigated bevacizumab combination with 5-FU-based chemotherapy in advanced colorectal cancer, the estimated incidence of GI perforation was reported to be around 1.5% (0–3.3%) [37]. Perforations seem to occur early in treatment, usually within 6 months after the start of bevacizumab, and can be localized anywhere along the GI tract [37]. Surgical intervention may be required, but is not always necessary. Concerns about surgical wound and anastomotic healing under bevacizumab treatment can justify a conservative approach in stable patients. Perforation rate was especially higher when the primary tumor was still intact or if a patient had received prior abdominal radiotherapy [37]. Other risk factors included the presence of peritoneal carcinomatosis, GI obstruction, gastric ulcer disease, acute diverticulitis, and chemotherapy-associated colitis [36, 37]. Many consider the presence of a colonic stent in situ as a contraindication for VEGF targeting agents, because there seems to be an increased risk of a perforation in the GI tract. However, none of these risk factors have been validated in multivariate analysis. Although GI perforations have also been described after the use of aflibercept and ramucirumab, the incidence is not so clear, because of the more recent introduction of these agents. It is believed by many that this is probably similar to the incidence after the use of bevacizumab. The contribution of VEGF inhibition to the development of GI perforation is incompletely understood. Several hypotheses have been proposed, but pathophysiological mechanisms are most likely multifactorial. Among others, VEGF inhibition can induce regression of normal blood vessels in the GI tract and can cause a decreased splanchnic blood flow due to a loss of nitric oxide release [38]. Delayed healing of chemotherapy-induced mucosal damage and development of cholesterol emboli syndrome may also be involved in pathogenesis [38].

4.4 Epidermal Growth Factor Receptor Inhibition: Cetuximab and Panitumumab

The epidermal growth factor receptor (EGFR, HER1, or ErbB1) is a glycoprotein receptor, comprising an extracellular ligand-binding domain, a transmembrane region, and an intracytoplasmic domain with tyrosine kinase activity. Ligand binding of the extracellular domain results in homodimerization or heterodimerization with other members of the EGFR family (HER2, HER3, HER4) and subsequent initiation of downstream signaling pathways by autophosphorylation. These downstream signaling cascades include the mitogen-activated protein kinase (MAPK) pathway and the phosphatidylinositol-3-kinase (PI3K) pathway. EGFR regulates cellular growth, differentiation, and survival, and abnormal EGFR activation can result in uncontrolled cell proliferation, which makes this receptor an attractive target for cancer treatment. Anti-EGFR-targeted agents include antibodies and tyrosine kinase inhibitors. They play an important role in the treatment of various cancers, either as monotherapy or in combination with chemotherapy. In colorectal cancer, the tyrosine kinase inhibitors are not used, because of low or no activity. However, the anti-EGFR monoclonal antibodies cetuximab (Erbitux, ImClone Systems, New York, NY, USA) and panitumumab (Vectibix, Amgen, Thousand Oaks, CA, USA) are frequently used in RAS wild-type tumors [39]. The clinically significant activity of cetuximab and panitumumab in metastatic colorectal cancer has been demonstrated by a number of phase III clinical trials [40]. In pancreatic cancer, the anti-EGFR tyrosine kinase inhibitor erlotinib has been approved in combination with gemcitabine, but is not widely used in Europe. Class-related adverse events are summarized in Table 4.2 and further explained in the following sections.

4.4.1 EGFR Inhibitor-Associated Skin Toxicity

Dermatologic side effects are the most common class-specific adverse event reported during anti-EGFR therapy. The rash has a typical appearance (acneiform eruption on the face, scalp, neck, shoulders, and upper trunk), is encountered most frequently in about 50–100% of treated patients, and occurs rapidly after starting the antibodies [41]. Other manifestations that usually occur later in the treatment include xerosis, leading to eczema and fissures, telangiectasia, hyperpigmentation, hair changes, and paronychia with pyogenic granuloma [41, 42].

The pathophysiology remains largely elusive. Most likely, the underlying mechanism is based on inhibition of the EGF receptor in the skin. EGFR is expressed in the basal epidermal cells, sebaceous glands, and hair follicle outer root sheath and hair shaft [43]. There are a lot of data in different tumors with the different agents, suggesting a correlation between the severity of skin toxicity and the antitumor efficacy of EGFR-targeted treatment [41, 44]. In the small EVEREST trial in chemorefractory colorectal cancer, it has been suggested that a stepwise increase in the dose of cetuximab (from weekly 250 mg/m^2 till 500 mg/m^2) may lead to

increased response rate, in patients with no or only a slight rash. However, this has never been validated in large prospective trials so that there is no standard recommendation in patients who do not develop rash to increase the dose of the anti-EGFR antibody [45].

EGFR inhibitor-related skin toxicity often causes cosmetic discomfort, pruritus, or pain, thereby compromising a patient's quality of life and potentially provoking noncompliance. Therefore, adequate treatment of skin symptoms is mandatory. Although we lack evidence-based data on the treatment, many experience-based guidelines have been published, which include topical treatment as well as systemic treatment with antihistamines and antibiotics [41, 42]. A multidisciplinary cooperation of the oncologist and dermatologist is necessary to provide an optimal treatment for each individual patient. Dermatologic symptoms induced by EGFR inhibitors are generally reversible after discontinuation of treatment.

4.4.2 EGFR Inhibitor-Induced Magnesium Wasting

In healthy subjects, serum magnesium (Mg^{2+}) levels are tightly regulated and kept within the 0.70–1.10 mmol/L range by variations in urinary Mg^{2+} excretion in response to altered intestinal Mg^{2+} uptake. After ultrafiltration in the kidney, magnesium is reabsorbed passively in the proximal tubule and the ascending limb of the loop of Henle. However, in the distal convoluted tubule, additional Mg^{2+} reabsorption is mediated by an active transport process through the activity of the transient receptor potential cation channel TRPM6. Magnesium deficiency (serum $Mg^{2+} < 0.70$ mmol/L) may manifest with symptoms of muscle dysfunction (tetany, weakness, ataxia, spasticity, tremor, and cramps), cardiovascular disorders (prolonged QT interval and cardiac arrhythmia), or neurocognitive dysfunction (convulsion, confusion, psychosis, agitation, delirium, and depression) [46].

Clinical trials with EGFR-inhibiting monoclonal antibodies have demonstrated the occurrence of drug-induced electrolyte disorders, such as hypomagnesemia and, in patients with severe hypomagnesemia, also hypocalcemia [46]. It has been suggested that EGFR inhibition induces a TRPM6 dysfunction, comparable to the one seen in patients with hereditary loss of functional mutations in the TRPM6 gene, characterized by urinary magnesium wasting [47, 48].

Most patients with grade 1–2 hypomagnesemia seem to be asymptomatic, although the interpretation is difficult in these heavily pretreated patients with advanced cancer. Patients with severe hypomagnesemia can also develop secondary hypocalcemia through induction of parathyroid hormone (PTH) resistance or suppression [47]. A prospective analysis in patients with colorectal cancer treated with anti-EGFR antibodies showed a decrease in serum Mg^{2+} concentrations in 97% of patients during treatment [47]. The incidence of grade 3–4 hypomagnesemia varies between 4.5 and 27% [46]. The median time to onset of hypomagnesemia is 99 days, and recovery of serum magnesium levels is usually achieved 4–6 weeks after discontinuation of EGFR inhibitors [46, 47]. Longer treatment duration with EGFR-blocking agents is associated with a higher risk of developing more severe

hypomagnesemia [47, 49]. Increasing age and higher baseline serum Mg^{2+} levels seem also to be related to enhanced renal magnesium wasting [47]. The available data show no difference in incidence and severity of hypomagnesemia between the cetuximab and panitumumab. The duration of treatment is an important factor that should be considered when evaluating the incidence in the different trials. The incidence of hypomagnesemia after a treatment with EGFR tyrosine kinase inhibitors seems to be very low, and this does not seem to be a clinical problem for the tyrosine kinase inhibitors.

Since symptoms of hypomagnesemia can easily remain unrecognized, serum Mg^{2+} levels should be measured regularly (every 4 weeks?) in patients receiving anti-EGFR antibodies. The management is based upon the grade of severity [50]. However, oral magnesium supplementation is not well tolerated, owing to diarrhea, and is often ineffective [47, 50]. Therefore, grade 1 hypomagnesemia requires no treatment, and it is suggested that only patients with grade 2 hypomagnesemia and risk factors such as age and a history of cardiac disease should be treated [50]. Patients should be treated with high doses of oral magnesium supplementation or weekly intravenous replacement (4 g magnesium sulfate). In patients with grade 3–4 hypomagnesemia, appropriate replacement therapy should be given due to the risk of cardiac arrhythmias [50]. This can be very challenging, since serum magnesium levels tend to fall back to the low values within 3–4 days after intravenous replacement and more frequent intravenous administration of magnesium sulfate is time-consuming and socially restricting [47, 50]. The best replacement strategy has yet to be determined. Dose reduction of anti-EGFR antibodies for hypomagnesemia has not been studied. A stop-and-go approach with anti-EGFR antibodies can be an alternative for patients with severe hypomagnesemia, without a large tumor burden [50].

4.4.3 EGFR Inhibitor-Associated Hypersensitivity Infusion Reactions

Allergic and anaphylactic reactions during anti-EFGR antibody administration can cause severe morbidity and a risk for fatal outcome. They are encountered more frequently with the chimeric antibody, cetuximab, than with the fully humanized antibody, panitumumab. In some colorectal cancer trials, up to 5% of the patients treated with cetuximab developed relatively severe hypersensitivity reactions, despite pretreatment with antihistamines [39]. In 0.1% outcome was fatal [51]. The incidence of allergic reactions seen with panitumumab is much lower, with an overall incidence around 3% and severe reactions in <1% [39, 51]. Up to 90% of severe reactions occur during the first dose of cetuximab [51]. More recently, it has been shown that premedication with antihistamines and corticosteroids, especially before the first administration of cetuximab, can reduce the incidence of severe infusion reactions. Therefore, prophylactic administration of antiallergic drugs is warranted prior to every cetuximab infusion, and patients should be monitored for at least 1 h after each cetuximab administration. Premedication before administration of panitumumab is not routinely recommended. The optimal prophylactic premedication to

prevent hypersensitivity reactions remains unclear but probably includes a corticosteroid and an antihistamine [52].

The pathophysiology of EGFR-associated hypersensitivity is incompletely understood. The presence of IgE antibodies against the galactose-α-1,3-galactose oligosaccharide may play a role in rapid infusion reactions to cetuximab, but it does not explain the mechanisms in more delayed reactions [53]. There are no data on possible risk factors of hypersensitivity to anti-EGFR antibodies.

In case of severe grade 3–4 hypersensitivity reactions, immediate interruption of the anti-EGFR antibody is required, followed by supportive care with administration of oxygen, corticosteroids, and antihistamines [51]. In the presence of hypotension or bronchospasm, the use of vasopressors, epinephrine, and bronchodilators may be necessary. In cases of mild to moderate grade 1–2 infusion reactions, infusion of anti-EGFR antibodies may be safely resumed at a slower infusion rate, after resolution of the allergic symptoms [54]. Because panitumumab has proven to be less allergenic compared to cetuximab, a switch to panitumumab could be a treatment option for patients who developed severe hypersensitivity reactions to cetuximab. Theoretically, there should be no crossover effect because the severe allergic reactions to cetuximab are believed to be directed against its murine component [51]. However, only scarce case reports are available that suggest this approach to be feasible and safe [51, 52].

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Gynecologic Cancer

5

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Abstract

Gynecologic tumors constitute an important part of cancer in women. There have been improvements in outcomes after surgery, chemotherapy, and radiation therapy; however, patients do experience significant treatment-related side effects.

Besides the classical cytotoxic agents and hormonal agents, used for many years, the development of newer molecular targeted and immunotherapeutic agents is currently an exciting area of interest in the care of patients with gynecologic malignancies.

Challenges are careful selection of patients for optimizing the combination of treatment modalities and drugs in order to obtain optimal efficacy. The latter depends on several factors: (1) the drug must be active as single agent against the particular tumor; (2) the drugs should have different mechanisms of action to minimize emergence of drug resistance; (3) the drugs should have a biochemical basis of at least additive and preferably synergistic effects; (4) the drugs chosen should have a different spectrum of toxicity so they can be used for maximum cell kill at full doses; and (5) the drugs chosen should be administered intermittently so that cell kill is enhanced and prolonged immunosuppression is minimized. This chapter gives an overview of the currently used treatment modalities in gynecologic cancer, their side effects, and their management.

This is an updated version of the chapter contributed by Sevilay Altintas, Dirk L.A.L. Schrijvers, and Jan B. Vermorken for the book "Side Effects of Medical Cancer Therapy" in 2013. The updates in this chapter were solely done by Sevilay Altintas and Dirk L.A.L. Schrijvers.

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M. A. Dicato, E. Van Cutsem (eds.), *Side Effects of Medical Cancer Therapy*,
https://doi.org/10.1007/978-3-319-70253-7_5

Keywords
Gynecologic cancer · Ovarian cancer · Endometrial cancer · Cervical cancer · Vulvar cancer · Gestational trophoblastic neoplasia · Chemotherapy · Hormonal therapy · Targeted therapy · Side effects

5.1 Introduction

Systemic therapies are playing an important role in the management of patients with gynecologic malignancies. The development in systemic therapy in various tumor types is discussed, mainly focusing on what is standard, but also some new developments in each of them are given.

In some of these malignancies, a new distinction has been made between different subtypes based on distinctive morphologic and molecular genetic features, which might lead to a more personalized treatment. Novel treatment strategies will be developed based on these characteristics (e.g., molecular targeted treatments), which will be accompanied by other and sometimes new forms of toxicity. To manage these new side effects, additional education and experience are essential.

5.2 Ovarian Cancer

Ovarian cancer is the most lethal gynecologic malignancy with an incidence rate of 12.6/100,000 women/year accounting for 44,149 women in 2012 and a mortality rate of 7.4/100,000 women/year accounting for 29,770 women in 2012 in the European Union [1].

In 2013, the World Health Organization updated the classification of ovarian cancer. Surface epithelial-stromal cancer is divided in epithelial ovarian cancer (EOC) such as serous adenocarcinoma, mucinous adenocarcinoma, endometrioid adenocarcinoma, clear cell adenocarcinoma, malignant Brenner tumor, transitional cell carcinoma (non-Brenner type), and stromal tumors (e.g., adenosarcoma, carcinosarcoma). In addition, sex cord-stromal tumors (e.g., granulosa tumors, Sertoli cell tumors), germ cell tumors, and metastatic cancer to the ovarium have been defined as separate entities [2].

In 2017, there has been an adaption of the International Federation of Gynecology and Obstetrics (FIGO) staging of ovarian, fallopian tube, and peritoneal cancer [3]. The classification applies to malignant ovarian neoplasms of both epithelial and stromal origin including borderline malignancies or of low malignant potential. The staging is surgical and most appropriately done by a well-trained gynecologic oncologist.

- Stage I ovarian or fallopian tube cancer is confined to the ovaries or the fallopian tubes. Surgical spill, capsule rupture before surgery, surface involvement by tumor cells, or presence of malignant cells in the ascites or peritoneal washings warrants a stage of IC classification.

- Stage II disease is classified as tumor involvement of one or both ovaries or fallopian tubes with pelvic extension below the pelvic brim or primary peritoneal cancer.
- Stage III disease is defined as tumor involvement of one or both ovaries or fallopian tubes or primary peritoneal carcinoma with cytological or histologically confirmed spread to the peritoneum outside the pelvis and/or metastasis to the retroperitoneal lymph nodes.
- Stage IV disease is defined as distant metastasis and includes patients with pleural effusion with positive cytology (stage IVA); parenchymal metastases and metastasis to extra-abdominal organs (including inguinal lymph nodes and lymph nodes outside the abdominal cavity) (IVB) [3].

Essential prognostic risk factors, related to the tumor are histology, grade, surgical stage and maximum diameter of residual disease after optimal debulking; and related to the patient are age, comorbidity, and performance status. Also the maximum diameter of residual disease after optimal debulking is an essential prognostic risk factor [3].

5.2.1 Treatment of Epithelial Ovarian Cancer

Surgery remains the principal treatment modality in the primary treatment of EOC. It is combined with chemotherapy in patients with more advanced or aggressive disease, where interval debulking after induction chemotherapy has become a valid treatment strategy. Surgery also has a place, after chemotherapy in selected patients with recurrent disease.

Based on preclinical and clinical information, various targets of interest (e.g., DNA repair mechanisms, growth factors and their receptors, angiogenic pathways and extracellular matrix, signal transduction pathways, cell survival pathways, and the proteasome) have been identified in EOC.

5.2.1.1 Chemotherapy

EOC is a chemosensitive disease, and many cytotoxic agents from different classes of drugs are active in this disease, such as alkylating agents (e.g., cyclophosphamide, ifosfamide, hexamethylmelamine), platinum compounds (e.g., cisplatin, carboplatin, oxaliplatin), taxanes (e.g., paclitaxel, docetaxel), anthracyclines (e.g., doxorubicin, epirubicin, pegylated liposomal doxorubicin [PLD]), antimetabolites (e.g., 5-fluorouracil, gemcitabine), vinca alkaloids (e.g., vinorelbine), topoisomerase I inhibitors (e.g., topotecan, irinotecan), topoisomerase II inhibitors (e.g., etoposide), and, more recently, the minor groove binder trabectedin.

Primary Treatment

Patients with stage IA-IB disease with bad prognostic characteristics (e.g., grade 2 serous/endometrioid type) can be offered 3–6 cycles of an intravenous (IV) taxane/carboplatin (TC)-based chemotherapy after surgery. Patients with a stage IA or IB grade 3 histology or stage IC should receive 3–6 cycles of TC-based chemotherapy after surgery [4].

The standard adjuvant chemotherapy approach for patients with stage II, III, or IV potentially resectable disease is intraperitoneal (IP) chemotherapy in optimally debulked stage II and stage III disease or six cycles of IV TC-based chemotherapy [4].

In patients with primary unresectable stage II, III, or IV disease, six cycles of TC-based chemotherapy can be given with an interval debulking before cycle 4 [4]. Recently, data of the addition of hyperthermic intraperitoneal chemotherapy (HIPEC) to interval cytoreductive surgery proved to be beneficial in terms of recurrence-free and overall survival in patients with stage III EOC [5].

In patients with a complete remission after primary chemotherapy, observation or a maintenance therapy with pazopanib or paclitaxel can be proposed [5]. In a randomized study, pazopanib maintenance therapy provided a median improvement of 5.6 months (hazard ratio [HR], 0.77) in progression-free survival in patients with advanced ovarian cancer who did not progress after first-line chemotherapy although overall survival data did not suggest any benefit [6].

The addition of maintenance paclitaxel compared to no further treatment did not improve progression-free or overall survival [7]. When comparing 3 or 12 cycles of maintenance paclitaxel, there was an improvement in progression-free survival but not in overall survival [8].

In patients with residual or progressive disease after or during adjuvant treatment, prognosis is bad and a clinical trial or second-line treatments can be proposed in combination with palliative care.

Recurrent Disease

The treatment of recurrent disease depends on the duration of the recurrence-free interval and is defined as platinum-resistant (<6 months) or platinum-sensitive (≥6 months) disease.

Patients with platinum-sensitive disease can be retreated with platinum-based regimens, and if possible, induction treatment may be followed by secondary cytoreductive surgery in combination with HIPEC. This last approach improves overall survival [9].

Other active regimens are combinations of carboplatin plus PLD, gemcitabine or topotecan, which are equally effective in terms of progression-free and overall survival [10], or the combination of PLD and trabectedin [11].

Patients with platinum-resistant disease can be treated with single-agent chemotherapy (e.g., PLD, topotecan, etoposide, gemcitabine, docetaxel, or weekly paclitaxel) with a clinical benefit in around 20% of patients, but prognosis remains poor.

5.2.1.2 Targeted Agents

Angiogenic Targeting Drugs

Bevacizumab

Bevacizumab, a monoclonal antibody against vascular endothelial growth factor (VEGF), which targets the angiogenic pathway, has been registered in different settings in the treatment of EOC.

Primary Treatment

After cytoreductive surgery, treatment with bevacizumab in addition to TC-based chemotherapy for up to six cycles of treatment followed by continued use of bevacizumab as single agent until disease progression, for a maximum of 15 months or until unacceptable toxicity, induces an increased progression-free survival [12] but no overall survival benefit in unselected patients. In patients with a high risk of progression, defined as stage IV disease, inoperable stage III disease, or suboptimally debulked (>1 cm) stage III disease, there was an overall survival benefit [13].

Recurrent EOC

Bevacizumab and carboplatin in combination with gemcitabine or paclitaxel has been registered for patients with recurrent platinum-sensitive epithelial ovarian, fallopian tube or primary peritoneal cancer, who have not received prior therapy with bevacizumab or other VEGF inhibitors or VEGF receptor–targeted agents, with an improvement in progression-free survival [14], although no overall survival benefit was shown [15].

In platinum-resistant recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who received no more than two prior chemotherapy regimens and who have not received prior therapy with bevacizumab or other VEGF inhibitors or VEGF receptor–targeted agents, the addition of bevacizumab to weekly paclitaxel, topotecan, or PLD improved progression-free survival but no overall survival compared to chemotherapy alone [16].

An important question remains whether bevacizumab has a role as standard treatment in patients with epithelial ovarian, fallopian tube or primary peritoneal cancer, considering the costs of these agents and its lack of improvement of overall survival, which has only been shown in patients with high risk disease.

Other Anti-angiogenic Drugs

Other anti-angiogenic drugs (e.g., pazopanib, nintedanib, cediranib, trebananib) either alone or in combination with chemotherapy have demonstrated activity in patients with EOC and different types of platinum sensitivity in phase II trials.

Cediranib was tested in 486 patients with relapsed platinum-sensitive EOC in a randomized double-blind, placebo-controlled phase III trial. Patients received up to six cycles of platinum-based chemotherapy and then entered a maintenance phase. In addition to chemotherapy, they received placebo during chemotherapy and then placebo only as maintenance, cediranib 20 mg once daily during chemotherapy and then placebo only as maintenance, or cediranib 20 mg once daily during chemotherapy and then cediranib 20 mg once daily as maintenance. Median PFS, the primary endpoint, was 8.7 months (95% confidence interval [CI] 7.7–9.4 months) in the chemotherapy-only arm and 11.0 months (95% CI 10.4–11.7 months) in the cediranib-maintenance arm (HR (95% CI) 0.56, (0.44, 0.72); $p < 0.0001$). Diarrhea, neutropenia, hypertension, and voice changes were significantly more common during chemotherapy with cediranib, and diarrhea, hypothyroidism, and voice changes were more common during maintenance. There was a poor compliance with cediranib mostly due to toxic effects [17]. However, there was no overall survival benefit and the application for the treatment of ovarian cancer was redrawn on 19 September 2016 [18].

PARP Inhibitors

Olaparib

Olaparib is a potent inhibitor of human poly(ADP-ribose) polymerase enzymes (PARP-1, PARP-2, and PARP-3) that are required for the efficient repair of DNA single-strand breaks. Olaparib binds to the active site of DNA-associated PARP. Hereby it prevents the dissociation of PARP and traps it on the DNA, thus blocking repair. In replicating cells, this leads to DNA double-strand breaks. Homologous recombination repair (HRR) can overcome these double-strand breaks but requires functional BRCA1 and BRCA2 genes. In the absence of functional BRCA1 or 2, HRR cannot be performed, leading to cell death.

Olaparib has been registered as maintenance treatment in adult patients with platinum-sensitive relapsed BRCA-mutated (germline and/or somatic) high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer, who are in response (complete or partial response) to platinum-based chemotherapy. Registration was based on a double-blind, placebo-controlled, phase II study in 265 patients with platinum-sensitive, relapsed, high-grade serous ovarian cancer who had received two or more platinum-based regimens and had a partial or complete response to their most recent platinum-based regimen. Treatment with olaparib translated in an improved median PFS (4.8 vs. 8.4 months; HR, (95%CI) 0.35, (0.25, 0.49 months); $p < 0.001$) [19].

The beneficial effect on progression-free survival of olaparib maintenance was confirmed in a phase III study in 295 patients with platinum-sensitive, relapsed ovarian cancer and a BRCA1/2 mutation who had received at least two lines of previous chemotherapy. Median progression-free survival was significantly longer with olaparib (19.1 months [95% CI 16.3–25.7 months]) than with placebo (5.5 months [95% CI 5.2–5.8 months]; HR 0.30 [95% CI 0.22–0.41], $p < 0.0001$) while side effects with olaparib were low grade and manageable [20].

Olaparib has been combined with chemotherapy and other targeted agents and tested in several randomized phase II studies.

When olaparib alone was compared in combination with carboplatin plus paclitaxel in 173 patients with platinum-sensitive, recurrent, high-grade serous ovarian cancer who had received up to three previous courses of platinum-based chemotherapy and who were progression-free for at least 6 months, there was an improvement of median PFS (9.6 vs. 12.2 months; HR (95%CI) 0.51 (0.34, 0.77); $p = 0.0012$), especially in patients with BRCA mutations (HR (95%CI) 0.21 (0.08, 0.55); $p = 0.0015$) [21].

Also the combination of olaparib with cediranib, an anti-angiogenic agent with activity against VEGF receptor (VEGFR1, VEGFR2, and VEGFR3), showed an improvement in median PFS compared to olaparib alone. In a randomized, open-label, phase II study, 90 patients with measurable platinum-sensitive, relapsed, high-grade serous or endometrioid ovarian, fallopian tube, or primary peritoneal cancer or those with deleterious germline BRCA1/2 mutations, the median PFS was 17.7 months in women treated with the combination compared with 9.0 months with olaparib alone (HR, (95%CI) 0.42, (0.23, 0.76); $p = 0.005$) [22].

These studies show that there might be a benefit of combining olaparib with other drugs in specific patient populations with EOC, but their effect should be studies in phase III studies.

Niraparib

Niraparib is an oral PARP 1/2 inhibitor and was tested as maintenance treatment for patients with platinum-sensitive, recurrent ovarian cancer. Patients were categorized according to the presence or absence of a germline BRCA mutation (gBRCA cohort and non-gBRCA cohort) and the type of non-gBRCA mutation. Patients in the niraparib group had a significantly longer progression-free survival compared to placebo, including 21.0 versus 5.5 months in the gBRCA cohort (HR 0.27, 95% CI 0.17–0.41), as compared with 12.9 months versus 3.8 months in the non-gBRCA cohort for patients who had tumors with homologous recombination deficiency (HRD) (HR 0.38, 95% CI 0.24–0.59) and 9.3 months versus 3.9 months in the overall non-gBRCA cohort (HR 0.45, 95% CI 0.34–0.61; $p < 0.001$ for all three comparisons). The most common grade 3 or 4 adverse events in the niraparib group were thrombocytopenia (in 33.8%), anemia (in 25.3%), and neutropenia (in 19.6%) [23].

Both olaparib and niraparib are registered in the EU for the treatment as monotherapy for the maintenance treatment in adult patients with platinum-sensitive relapsed BRCA-mutated (germline and/or somatic) high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete response or partial response) to platinum-based chemotherapy.

Rucaparib

Rucaparib is another PARP inhibitor, that showed activity in phase II studies in patients with high-grade ovarian cancer and a deleterious germline or somatic BRCA1 or BRCA2 (BRCA1/2) mutation with platinum-sensitive, resistant, or refractory disease. It induced an overall response rate of 53.8% (95% CI 43.8–63.5); 8.5% and 45.3% of patients achieved complete and partial responses, respectively. The median duration of response was 9.2 months (95% CI, 6.6–11.6 months), most frequently reported side effects were nausea, asthenia/fatigue, vomiting, and anemia. The most common grade ≥3 treatment-emergent adverse event was anemia [24].

Folate Receptor-α

Folate receptor-α is highly expressed in ovarian carcinoma and largely absent from normal tissue. Farletuzumab, a humanized monoclonal antibody that binds to folate receptor-α, was tested in a double-blind, randomized phase III study in 1100 patients with platinum-sensitive ovarian cancer.

They were randomized to six cycles of TC-based chemotherapy and farletuzumab 1.25 mg/kg, farletuzumab 2.5 mg/kg, or placebo. PFS, the primary endpoint of the study, was not different among the three groups as was overall survival. In a pre-specified subgroup, baseline CA-125 levels not more than three times the upper limit of normal correlated with longer PFS (HR 0.49; $p = 0.0028$) and overall survival (HR 0.44; $p = 0.0108$) for farletuzumab 2.5 mg/kg versus placebo [25].

Epidermal Growth Factor Receptor (EGFR) Targeting Drugs

In ovarian cancer, EGFR is overexpressed in 10–70% with an average of 48% of ovarian tumors. The EGFR can be influenced by monoclonal antibodies (e.g., cetuximab) or small molecules (e.g., gefitinib, erlotinib, lapatinib), and they have been tested in several phase II studies with or without chemotherapy in patients with EOC [26].

Monoclonal Antibodies

Cetuximab

In several phase II studies, cetuximab scheduled as 400 mg/m^2/week followed by 250 mg/m^2/week was combined with chemotherapy in patients with ovarian cancer. There was no indication that adding cetuximab to chemotherapy had a positive effect on PFS compared to data from chemotherapy alone [27, 28].

EGFR Tyrosine Kinase Inhibitors

Single-agent gefitinib [29], gefininib [30], or lapatinib [31] did not show activity in patients with recurrent EOC.

HER2 Receptor Targeting Drugs

HER2 receptor expression in ovarian cancer has been variable and ranges from 1.8% to 35% [32]. The HER2 receptor can be influenced by monoclonal antibodies or tyrosine kinase inhibitors, and some have been tested in patients with ovarian cancer (e.g., trastuzumab, pertuzumab, lapatinib) with limited effect, although in patients with HER2 overexpression tumors, the results may be better.

5.2.1.3 Immunotherapy

Several studies are determining the place of immunotherapy in patients with EOC since patients with a robust immune response, as documented by the presence of lymphocytes infiltrating within their tumor, have increased survival and better response to chemotherapy [33].

Adoptive cell immunotherapy in EOC, with the isolation and multiplication of HLA-restricted tumor-infiltrating lymphocytes (TILs), and MHC-independent immune effectors such as natural killer (NK) and cytokine-induced killer (CIK) have been tested in patients with advanced EOC. It is supposed that these kinds of treatments have their best benefit in settings of low tumor burden, minimal residual disease, or maintenance therapy [34].

Overexpression of the PD-1 and ligand PD-L1 has been demonstrated in ovarian cancer and may hinder an effective antitumor immune response. Check point inhibition with monoclonal antibodies against programmed death receptor-1 (PD-1) (e.g., nivolumab, pembrolizumab) or its ligand PD-L1 (avelumab, BMS-936559) has been tested in EOC and induced a disease control in 23–55% of patients with recurrent EOC [35].

Indoleamine 2,3-dioxygenase-1 (IDO1) is another key regulator of immune tolerance in ovarian cancer. Epacadostat, an IDO1 enzyme inhibitor was compared with tamoxifen in patients with biochemical-only recurrence (CA-125 elevation) following complete remission after first-line chemotherapy for advanced EOC, primary peritoneal, or fallopian tube cancer. Median PFS was 3.75 months for epacadostat versus 5.56 months for tamoxifen (HR 1.34, 95% CI 0.58–3.14; p = 0.54). The most common treatment-emergent adverse event was fatigue (epacadostat, 36.4%; tamoxifen, 40.0%). Immune-related adverse events, observed with epacadostat only, were primarily rash (18.2%) and pruritus (9.1%). Epacadostat did not show significant differences in efficacy compared to tamoxifen [36].

Abagovomab is an anti-idiotypic antibody against OC125, that recognizes the tumor-associated antigen CA-125 and induces a specific immune response, both humoral and cellular. It was tested in 888 patients with stage III–IV ovarian cancer in complete clinical remission after primary surgery and platinum- and taxane-based chemotherapy but was not able to prolong relapse-free or overall survival [37].

Based on the current data it is not possible to make a definitive statement of the use of immunotherapy in patients with EOC.

5.2.1.4 Hormonal Treatment

Anti-estrogens (e.g., tamoxifen), progestin (e.g., medroxyprogesterone acetate), and aromatase inhibitors have all been used in patients with recurrent EOC.

In a selected group of patients, responses have been reported and recently, a randomized trial compared the use of tamoxifen with chemotherapy in patients with platinum-resistant EOC. Median PFS on tamoxifen was 8.3 weeks (95% CI 8.0–10.4 weeks) compared with 12.7 weeks (95% CI 9.0–16.3 weeks) on chemotherapy (HR 1.54; 95% CI 1.16–2.05; log-rank p = 0.003), although there was no difference in OS between the treatment arms. Toxicity was higher in patients treated with chemotherapy [38].

5.2.2 Treatment of Non-epithelial Ovarian Cancer

Non-epithelial ovarian cancers are rare tumors and are often difficult to diagnose. They are approached if they were EOC, unless tumor marker patterns (e.g., (beta) β-human chorionic gonadotropin (hCG), alpha-fetoprotein (AFP), lactate dehydrogenase (LDH)), clinical signs (e.g., pregnancy signs, virilization, blood loss), and clinical findings (e.g., ovarian mass and endometrial thickening) do suggest a germ cell tumor (~5% of ovarian tumors, but >75% in young patients) or a sex cord-stromal tumor (~5% of ovarian tumors).

Considering the chemosensitivity of germ cell tumors, fertility-sparing surgery is recommended. About two-thirds are stage I disease, and in low-risk disease only careful follow-up after surgery is required. In high-risk disease and in more advanced

cases, a combination chemotherapy regimen of bleomycin, etoposide, and cisplatin (BEP) is recommended.

In patients with early-stage sex cord-stromal tumors, which comprise a variety of different tumors, including granulosa cell tumors (adult and juvenile types) and the Sertoli-Leydig cell tumors, no adjuvant chemotherapy is recommended. In higher-risk situations of granulosa cell tumors, such as a ruptured ovary or higher stage, adjuvant chemotherapy with etoposide and cisplatin (EP) or BEP might be considered [39].

In recurrent disease, the TC combination has shown activity, and early reports (mostly case reports) on the potential usefulness of bevacizumab and tyrosine kinase inhibitors (e.g., imatinib mesylate) are appearing.

Hormonal therapies including tamoxifen, progestogens, luteinizing hormone-releasing hormone (LHRH) analogues, and aromatase inhibitors have all been used with variable outcomes [40].

Carcinosarcomas previously called malignant mixed Müllerian tumors (MMMTs), which may occur in the ovary but also in the uterus, should be considered as malignant epithelial tumors, not as sarcomas, and treated as such. Adjuvant therapies are indicated in all cases, even in stage I. Based on the two components that are observed, there has been a debate about how to treat them with chemotherapy optimally—whether to use the TC regimen (as in EOC), which is reasonably well tolerated or to use (also) anthracyclines and/or ifosfamide.

5.3 Cancer of the Uterine Body

Cancer of the endometrium is the most common gynecologic malignancy in the industrialized world, occurring in 80–90% of postmenopausal women (median age 63 years), with 5% occurring in women younger than 40 years old. Its incidence rate in the European Union is 17.9/100,000 women/year accounting for 64,331 women in 2012, and its mortality rate is 3.3/100,000/year accounting for 14,680 women [1].

The main etiologic factor is unopposed/excessive estrogen exposure, and predisposing factors include nulliparity, early menarche/late menopause, obesity, diabetes mellitus, hypertension, and treatment with tamoxifen. Genetic susceptibility includes the Lynch type II syndrome.

Uterine cancers comprise malignant epithelial carcinomas (90%) and malignant mesenchymal sarcomas.

- Epithelial carcinomas are grouped into pure endometrioid carcinoma; and serous, clear cell, or undifferentiated carcinoma or carcinosarcoma.
- Malignant mesenchymal sarcomas are grouped in low-grade endometrial stromal sarcoma (ESS), high-grade ESS, undifferentiated uterine sarcoma or uterine leiomyosarcoma [41].

Staging of epithelial endometrial cancers is based on the TNM and FIGO classification [3].

- In stage I, the disease is confined to the corpus uteri
- In stage II disease, the tumor invades the cervical stroma

- In stage III disease, the tumor shows local extension and/or regional spread to lymph nodes
- In stage IV disease, the tumor invades the bladder or bowel mucosa (IVA) or presents with distant metastasis (IVB) [3].

Essential prognostic factors are the depth of the myometrial invasion, the grade of differentiation, tumor cell type, and lymphovascular space invasion.

Uterine sarcomas are classified according to TNM and FIGO [3]. In stage I, the disease is limited to the uterus; in stage II disease, it extends beyond the uterus within the pelvis; in stage III disease, the tumor involves abdominal tissues or has spread to regional lymph nodes; and in stage IV disease, the tumor invades the bladder or bowel mucosa (IVA) or presents with distant metastasis (IVB) [3].

Contrary to EOC, most patients with endometrial cancer are diagnosed in early stages because of abnormal uterine bleeding as the presenting symptom (90% of cases).

5.3.1 Endometrial Carcinoma

In patients with endometrial carcinoma limited to the uterus and who are able to undergo surgery, a total hysterectomy and bilateral salpingo-oophorectomy with surgical staging is indicated. In patients with localized disease who are not candidates to surgery due to comorbidities, radiotherapy (external beam radiotherapy [EBRT] or brachytherapy) is a treatment option.

Adjuvant treatment depends on the findings during surgical staging.

In patients with stage I disease with an invasion depth less than 50% and a grade 1, 2, or 3 without adverse risk factors defined by lymphovascular invasion, tumor size, lower uterine segment or surface cervical surface invasion, observation or brachytherapy may be proposed.

In patients with grade 2 stage I disease with adverse risk factors, brachytherapy with or without EBRT is standard treatment; and in patients with grade 3 disease with an invasion depth of equal or more than 50% of the myometrium, adjuvant chemotherapy may be added to radiotherapy.

In patients with grade 1 and 2 stage II disease, brachytherapy and/or EBRT is indicated as adjuvant treatment while in patients with grade 3 disease, EBRT with or without brachytherapy and systemic therapy is indicated.

In patients with stage III or IV disease, adjuvant systemic treatment is indicated with or without radiotherapy [41].

In patients with distant metastasis, a palliative hormonal or chemotherapeutic treatment can be discussed with the patient, in combination with palliative care.

5.3.1.1 Chemotherapy

Chemotherapy has a place as adjuvant treatment in patients with high-risk disease or in patients with recurrent/metastatic disease failing hormonal treatment; in those with rapidly progressive disease or those known to have PR-negative tumors. Among the different classes of cytotoxic agents, platinum compounds, anthracyclines, and taxanes are most commonly used [42].

In patients with stage III disease, adjuvant chemotherapy with carboplatin and paclitaxel is considered the preferred adjuvant treatment. However only one of three randomized trials comparing adjuvant radiotherapy alone versus adjuvant chemotherapy alone showed a benefit in terms of progression-free and overall survival, while in the two other trials including patients with early stage disease, chemotherapy did not induce an overall survival benefit [44].

If chemotherapy is indicated in patients with recurrent or metastatic disease, the combination of carboplatin and paclitaxel is the preferred regimen, taking into account toxicity versus activity. Other combinations such as doxorubicin with cisplatin, carboplatin with docetaxel, or doxorubicin plus paclitaxel have shown activity while the triple combination of doxorubicin, cisplatin, and paclitaxel was more toxic and not better in terms of overall survival compared to carboplatin and paclitaxel.

Doublets seem to be more active than single-agent chemotherapy. Single agents with activity in endometrial carcinoma are cisplatin, carboplatin and oxaliplatin, doxorubine and PLD, docetaxel, paclitaxel and albumin-bound paclitaxel, ixabepilone, topotecan, and ifosfamide [41, 45].

5.3.1.2 Hormonal Therapy

Hormonal therapy has no place in the adjuvant treatment of patients with endometrial cancer.

In the setting of recurrent/metastatic disease, hormonal therapy is the first-choice treatment to improve survival and quality of life (QoL). Overall the toxicity profile of hormonal therapies is more favorable than that of cytotoxic chemotherapy, and contrary to cytotoxic chemotherapy, hormonal therapy can be given for a longer period of time, generally without cumulative and increasing toxicity.

Progestins

Progestins (e.g., medroxyprogesterone acetate, megestrol acetate) have been the mainstay of hormonal treatment for many years. They may induce responses in a substantial number of patients, particularly in patients with PR-positive disease compared to PR-negative cancers (37% vs. 8%) [46, 47]. Nevertheless, these agents sometimes can be associated with significant adverse effects, which may have a negative impact on the QoL.

The type of progestin and the route of administration do not seem to be of major importance; in one GOG trial in which two dosages of orally administered medroxyprogesterone acetate were compared (200 mg/day vs. 1000 mg/day), the lower dose proved to be sufficient for an adequate antitumor effect [47].

Estrogen Pathway Modifying Drugs

Tamoxifen [48] and aromatase inhibitors (e.g., letrozole) [49] are good alternatives either as primary treatment or in those progressing on progestins. They induce response rates in around 10% of patients with a median PFS of between 2 and 7 months.

5.3.1.3 Targeted Therapy

Loss-of-function mutations of PTEN are common and appear to be important in the pathogenesis of type I endometrial carcinomas. Loss of PTEN causes deregulated phosphatidylinositol 3-kinase/serine-threonine kinase/mammalian target of rapamycin (PI3K/Akt/mTOR) signaling, which may provide neoplastic cells with a selective survival advantage by enhancing angiogenesis, protein translation, and cell cycle progression.

Angiogenesis Targeting Agents

Treatment of patients with recurrent/metastatic endometrial cancer with angiogenesis targeting agents showed limited response rates (e.g., bevacizumab, 13% [50]; temsirolimus, 14% [51]; erlotinib, 12.5% [52]; everolimus, 21% [53]).

Different combinations with chemotherapy or combinations of targeted agents yielded higher response rates (e.g., paclitaxel + carboplatin + bevacizumab, 73% [54]; bevacizumab + temsirolimus, 24.5% [55]; everolimus + letrozole, 32% [56]), but their effect should be evaluated in randomized trials.

HER2

HER2 amplification or overexpression has been demonstrated and linked to prognosis in endometrial cancer. Single-agent trastuzumab (4 mg/kg week 1, then 2 mg/kg weekly) was tested in 34 pretreated patients with HER2-positive endometrial carcinoma. Two deaths on treatment were considered possibly related to trastuzumab. One patient developed an infusion reaction and died from cardiac arrest 1 week after infusion, and the second patient suffered a myocardial infarction during her first course of therapy. There were no objective responses [57].

5.3.2 Uterine Sarcomas

Uterine sarcomas, although far less common than endometrial carcinomas, exhibit two features that increase the need for systemic therapy: a recurrence rate of at least 50%, even in stage I disease and a high propensity for distant failure.

Most experience has been gained with chemotherapy in the advanced setting, and this is the standard treatment in fit patients with metastatic uterine sarcoma.

Activity has been reported with single-agent doxorubicin, epirubicin, PLD, dacarbazine, gemcitabine, temozolomide, eribulin, vinorelbine, trabectedin, and docetaxel. Active combinations are the combinations of doxorubicin with olaratumab, ifosfamide, or dacarbazine; and of gemcitabine with docetaxel, dacarbazine, or vinorelbine [41].

For low-grade ESS and hormone receptor positive (ER/PR) uterine leiomyosarcoma, megestrol acetate, medroxyprogesterone acetate, aromatase inhibitors, and GnRH analogs may be used [41].

5.4 Cancer of the Uterine Cervix

Cervical cancer is the second most common malignancy for women worldwide and represents the third most common cause of female mortality, responsible for about 266,000 deaths in 2012.

In the European Union, the incidence rate was 11.3/100,000 women/year accounting for 33,354 women in 2012 and a death rate of 3.7/100,000 women/year accounting for 12,996 women [1].

High-risk persistent infection with sexually transmittable human papillomavirus is responsible for nearly all cases of cervical cancer. Therefore, risk factors for cervical cancer are the same as those for sexually transmitted disease, including early age at onset of sexual activity, multiple pregnancies, and multiple sexual partners. Also tobacco smoking is an important (co)factor for cervical cancer.

In those countries where adequate screenings programs are in place, the incidence and mortality have markedly decreased. For this reason, the mortality is ten times higher in developing countries, where approximately 80% of new cases occur [58].

In countries with adequate screening programs, squamous carcinoma of the cervix has decreased in the past decades, while the number of adenocarcinomas has increased and now comprises 20–25% of all cervical cancers. Other epithelial tumors of the cervix are adenosquamous carcinoma, glassy cell carcinoma, adenoid cystic carcinoma, adenoid basal epithelioma (carcinoma), neuroendocrine tumors, carcinoid tumors, and mixed epithelial and mesenchymal tumors and sarcomas (LMS and ESS), while primary cervical melanoma occurs rarely.

The TNM/FIGO staging system is based on clinical evaluation; roentgenographic examination of the chest, kidneys, and skeleton; and endocervical curettage and biopsy [3].

- Stage I disease is confined to the cervix
- Stage II disease shows tumor invasion beyond the uterus but not to the pelvic wall or to lower third of the vagina
- In stage III disease, the tumor involves the lower third of the vagina, extends to the pelvic wall, causes hydronephrosis or non-function kidneys, or presents with regional lymph node invasion
- In stage IV disease, the tumor invades mucosa of the bladder or rectum, extends beyond the true pelvis (IVA), or presents with distant metastatic disease (IVB).

Prognostic factors are unilateral versus bilateral disease, parametrial invasion, invasion to the side wall, the size of the tumor, lymph node invasion, and positive surgical margins [3].

In the last 20 years, numerous advances have been made in the medical management of cervical cancer, including preventive vaccination, and the integration of chemotherapy in the treatment of various stages of cervical cancer.

In patients with early stage I disease, who require a non-fertility-sparing intervention, a radical hysterectomy and pelvic lymph node dissection with or without para-aortic lymph node sampling or pelvic EBRT with brachytherapy is indicated [59].

Patients with stage IB–IIA disease are treated by radical hysterectomy and pelvic lymph node dissection plus para-aortic lymph node sampling or definitive chemoradiation or chemoradiation followed by hysterectomy.

Patients with locally advanced disease (stages IIB–IVA) and basically any stage (except stage IVB) with positive lymph nodes are treated with concurrent chemoradiation [57].

For patients with recurrent and/or metastatic cervical cancer, several options are available (surgery, radiation, chemotherapy, or palliative care only), depending on the specific situation. However, treatment of metastatic disease so far has remained palliative at best [58].

5.4.1 Chemotherapy

Since 1999, the standard primary treatment for patients with locally advanced cervical cancer is concurrent cisplatin-based chemotherapy with radiation therapy [58, 60] with an absolute benefit at 5 years of 6% compared to radiotherapy alone (60% → 66%). The magnitude of benefit was significantly higher in stages I to IIB than in the higher stages [60]. The improvement in stage III/IVA was only 3%, while for stage I–IIA this was 10%.

The majority of recurrences after concurrent chemoradiation are at distant sites; only a small percentage fail only within the pelvis.

In patients with pelvic recurrent disease, pelvic surgery should be considered in selected cases of central pelvic recurrence, and salvage radiotherapy should be considered in patients with a pelvic recurrence without prior irradiation. Systemic therapy (or only best supportive care) should be considered in the other cases.

Chemotherapy may be given in patients with recurrent/metastatic cervical cancer. Platinum-based therapies are most effective, and cisplatin seems more active than carboplatin or iproplatin. When higher dosages of platinum or platinum-based combinations are used, this leads to more response, but also more toxicity, without an impact on survival; therefore, a dose 50 mg/m^2, administered every 3 weeks, became standard.

Other chemotherapeutic agents showing activity in this disease are the taxanes (e.g., paclitaxel, docetaxel), the topoisomerase I inhibitors (mainly topotecan), the vinca alkaloids (e.g., vinorelbine), and the antimetabolites (e.g., fluorouracil, gemcitabine) [59].

In a direct comparison of cisplatin versus cisplatin plus paclitaxel (GOG study 169), there was gain in PFS for the combination (not in overall survival) [61], but when four different combinations were compared in GOG protocol 204 (cisplatin

plus paclitaxel or topotecan, or vinorelbine or gemcitabine), paclitaxel/cisplatin showed a trend for having a better response and PFS, but no significant differences in overall survival were observed [62].

5.4.2 Targeted Therapy

5.4.2.1 Anti-angiogenic Agents

Anti-angiogenic agents have activity in patients with advanced/recurrent cervical cancer, but only bevacizumab, a monoclonal antibody against VEGF, has been introduced in clinical practice in patients with advanced cervical cancer [63, 64].

The combination of anti-angiogenic agents in combination with chemotherapy and radiotherapy for localized disease is feasible and in a phase II studies, a high 2-year overall survival rate was reported [65, 66]. However, its place in clinical practice has been determined in phase III trials.

Bevacizumab, in combination with paclitaxel and cisplatin or with paclitaxel and topotecan in patients who cannot be treated with cisplatin-based therapy, has been registered for the treatment of persistent, recurrent, or metastatic carcinoma of the cervix [63]. This registration was based on a randomized phase III study (GOG-0240) which compared the addition of bevacizumab in 452 patients with persistent, recurrent, or metastatic carcinoma of the cervix to paclitaxel plus cisplatin or paclitaxel plus topotecan. Patients in the experimental arm were treated with bevacizumab 15 mg/kg IV every 3 weeks. The combination of bevacizumab with chemotherapy compared to chemotherapy alone led to an improvement in overall survival, the primary endpoint, in favor of the bevacizumab combination with a median overall survival of 17.0 versus 13.3 months (HR (98%CI) 0.71, (0.54, 0.95); $p = 0.004$). The addition of bevacizumab to chemotherapy led to a higher incidence of grade 2 or higher hypertension (25% vs. 2%), grade 3 or higher thromboembolic events (8% vs. 1%), and grade 3 or higher gastrointestinal fistulas (3% vs. 0%) [64].

Several small molecules that inhibit the VEGF receptor (VEGFR) have been tested in patients with cervical cancer.

Pazopanib showed single-agent activity in cervical cancer that was better than lapatinib or the combination pazopanib/lapatinib. Pazopanib improved PFS (HR, (90%CI) 0.66 (0.48, 0.91); $p = 0.013$) and overall survival (50.7 vs. 39.1 weeks; HR, (90%CI) 0.67, (0.46, 0.99); $p = 0.045$) compared to lapatinib alone. The most frequent side effect was diarrhea (11% pazopanib, 13% lapatinib) [67].

Another angiogenic agent, sunitinib, proved to be ineffective when used as single agent with development of vaginal fistula in 26.3% of patients [68].

The combination of cediranib and TC was superior compared to carboplatin and paclitaxel alone in 69 patients with metastatic/recurrent cervical cancer in terms of PFS (6.7 vs. 8.1 months, HR (80%CI) 0.58 (0.40, 0.85); $p = 0.032$). Grade 3 or worse adverse events that occurred in the cediranib group more than 10% of patients were diarrhea (16% vs. 3%), fatigue (13% vs. 6%), leukopenia (16% vs. 9%), neutropenia (31% vs. 11%), and febrile neutropenia (16% vs. 0%). The incidence of grade 2–3 hypertension was higher in the cediranib group (34% vs. 11%) [69].

Temsirolimus, an mTOR inhibitor, showed clinical activity in 37 evaluable patients with metastatic/recurrent cervical cancer with a partial response rate of 3.0% and a 57.6% stable disease rate. The median PFS was 3.52 months (95%CI 1.81, 4.70). Adverse effects were mild to moderate and similar to those observed in other temsirolimus studies [70].

These data show that anti-angiogenic agents are active in patients with recurrent/metastatic cervical cancer but their treatment comes at a cost of toxicity that differs for different agents.

The combination of erlotinib with cisplatin and radiotherapy has been evaluated in 36 patients with stage IIB to IIIB cervical cancer. They were treated with erlotinib (150 mg/day) 1 week before and in combination with cisplatin (40 mg/m^2 q weekly for five cycles) during radiotherapy [45 Gray (Gy) in 25 fractions], followed by brachytherapy (4 fractions at a dose of 6 Gy weekly). This treatment regimen was feasible, and 34 patients achieved a complete response. The 2-year and 3-year cumulative overall and PFS survival rates were 91.7% and 80.6% and 80% and 73.8%, respectively [71].

Phase III studies will be needed to show superiority of this regimen compared to standard cisplatin-based treatment in this patient group.

5.4.2.2 Epidermal Growth Factor Receptor (EGFR) Pathway Targeting Drugs

EGFR is frequently overexpressed in cervical cancer, suggesting that EGFR blockade may be a promising treatment approach.

Cetuximab, a monoclonal antibody against EGFR, has been tested in patients with locally advanced/recurrent/metastatic disease.

When used as single agent in patients with recurrent disease, it showed no responses, a PFS of 1.97 months, and an overall survival of 6.7 months [72].

The combination with cisplatin was feasible, but the response rate was only 9% in chemotherapy-pretreated patients and 16% in chemotherapy-naïve patients [73].

When combined with cisplatin and topotecan , excessive toxicity was encountered with grade 3–4 neutropenia (72%), grade 3–4 thrombocytopenia (61%), grade 3 anemia (44.5%), febrile neutropenia (28%), grade 3–4 skin reactions (22%), renal toxicity (11%), and pulmonary embolism (11%). Five (28%) patients died during the treatment including three treatment-related deaths. The response rate was 32%, the median PFS 172 days, and the overall survival 220 days [74].

The combination of cetuximab (cetuximab 400 mg/m^2 loading dose and then 250 mg/m^2) plus weekly cisplatin (30 or 40 mg/m^2) and radiotherapy was feasible in a phase I study, provided no extended field radiation therapy (EFRT) was used. This last treatment was too toxic with grade 3 or 4 small bowel obstruction, embolism, mucositis, mucositis with hypokalemia, pain with headache, and platelets with mucositis and headache [75].

In a randomized phase II study, 78 patients with FIGO stage IB2-IIIB cervical cancer were treated with either cisplatin-based radiochemotherapy alone ($n = 38$) or with a 6-week course of weekly cetuximab ($n = 40$). Brachytherapy was given to the pelvic mass. The addition of cetuximab did not improve the PFS at 24 months, which was the primary endpoint of this trial [76].

These data do not support the use of cetuximab in unselected patients with cervical cancer, and biomarkers are necessary to identify patients that might benefit of a cetuximab treatment.

5.4.3 Immunotherapy

Immunomodulation has been evaluated in patients with cervical cancer.

In a Japanese placebo-controlled randomized phase III study, 249 patients with locally advanced stage IIB–IVA squamous cell cervical cancer were randomly assigned to receive Z-100, a hot-water extract from human bacillus tuberculosis containing polysaccharides subcutaneously, or placebo together with standard (chemo)radiotherapy treatment.

There was a positive trend in overall survival, the primary endpoint, although no statistically significant improvement, with a 5-year survival rate of 75.7% in the Z-100 group and 65.8% in the placebo group (HRdeath, (95%CI) 0.65, (0.40–1.04) $p = 0.07$). Subgroup analysis showed a significant survival benefit in patients with stage III disease [77].

Several phase I/II immunomodulatory trials are ongoing in cervical cancer including checkpoint inhibitors either as single agent [e.g., anti-PD-1 antibodies pembrolizumab (NCT02628067) and nivolumab (NCT02488759)] or in combination with radiotherapy [e.g., anti-CTLA-4 antibody ipilimumab (NCT01711515) or combinations of immunomodulatory agents (durvalumab, an anti-PD-L1 antibody in combination with tremelimumab, an anti-CTLA-4 antibody); cancer vaccines to elicit a T cell immune response against tumor-specific or tumor-associated antigens (VGX-3100 and INO-9012), a DNA construct inducing interleukin 12 (NCT02172911)] and adoptive cell therapy in patients with HPV-related cancer with their own hematologic cells (NCT01585428) or genetically engineered T cells to target HPV16 E6 (NCT02280811, NCT02379520).

Recently, the activity of Pembrolizumab was reported in patients with advanced, programmed death ligand 1-Positive cervical cancer (KEYNOTE-028 Trial). The overall response rate in 24 patients was 17% (95% CI, 5–37%); and the median duration of response in patients with a partial response was 5.4 months (4.1–7.5 months) [78].

5.5 Carcinoma of the Vulva

Malignant tumors of the vulva are rare (less than 5% of all cancers of the female genital tract). The majority of malignant vulvar cancers are squamous cell carcinomas, but melanoma, basal cell carcinoma, adenocarcinomas, and sarcomas also may occur. Finally, the vulva may be secondarily involved with malignant disease originating in the bladder, anorectum, or other genital organs [79].

The staging of vulvar carcinoma is based on the TNM and FIGO classification [3].

- Stage I disease is confined to the vulva or vulva and peritoneum
- Stage II disease is a tumor invading the lower third of the urethra, the lower third of the vagina or the anus.

- In stage III disease regional lymph node invasion is present without local invasion of the upper 2/3 of the urethra, the upper 2/3 of the vagina, the bladder or rectal mucosa or fixation to the pelvic bone.
- Stage IV disease is defined as fixed or ulcerated regional lymph nodes or local invasion of the upper 2/3 of the urethra, the upper 2/3 of the vagina, the bladder or rectal mucosa or fixation to the pelvic bone (IVA); or distant metastatic disease (IVB).

Essential prognostic factors are the number, size, and extracapsular tumor growth of lymph nodes.

Treatment consists of radical surgery (or a more individualized therapy with less morbidity, but retaining the curative potential of the radical vulvectomy operation) and postoperative irradiation in selected patients at high risk for locoregional failure.

The addition of chemotherapy concurrent to radiation therapy was heavily influenced by advances in the treatment of cervical cancer and squamous cell carcinoma of the anal canal. For those patients who have unresectable primary disease or with palpably suspicious, fixed, and/or ulcerated lymph nodes preoperatively, chemoradiation is the preferred option. Drugs that have been used for that are 5-fluorouracil or cisplatin alone or combined. Such an approach is also attractive when it can be followed by tailored surgery, to avoid ultra-radical surgical procedures [79, 80].

The role of chemotherapy in the metastatic disease setting is disappointing because of the fact that patients with vulvar cancer tend to be older, making them poor candidates for cytotoxic therapy, because of concomitant diseases that increase the likelihood for significant adverse effects. Nevertheless, two EORTC Gynecological Cancer Cooperative Group studies showed therapeutic activity of the bleomycin, methotrexate, and lomustine (BMC) regimen, inducing a response rate of the order of 60% in the neoadjuvant setting [81, 82].

5.6 Gestational Trophoblastic Disease

Gestational trophoblastic neoplasia (GTN) is a chemosensitive disease [83]. When in the 1950s the first patient with metastatic choriocarcinoma was successfully treated with chemotherapy at the National Cancer Institute, the late Arthur T. Hertig, professor of pathology at Harvard Medical School, called this God's first cancer and man's first cure [84].

GTN comprises a heterogeneous group of interrelated lesions that arise from abnormal proliferation of placental trophoblast. GTN lesions are histologically distinct malignant lesions that include invasive hydatidiform mole, choriocarcinoma, placental site trophoblastic tumor, and epithelioid trophoblastic tumor. GTN often arises after molar pregnancies but can also occur after any gestation, including miscarriages and term pregnancies.

In the United States, hydatidiform moles are observed in approximately 1/600 therapeutic abortions and 1/1000–2000 pregnancies [84].

The treatment of these patients should be individualized. Once the pretreatment evaluation is completed and the extent of disease determined, the patient should be assigned a stage (FIGO stages I–IV) and a prognostic score, based on age,

antecedent pregnancy, interval from index pregnancy, pretreatment serum human chorionic gonadotropin (hCG), largest tumor size, site of metastases, number of metastases, and whether or not the patient had failed on previous chemotherapy [85]. A risk score of 6 or less indicates low-risk GTN, whereas a score of 7 or more identifies high-risk disease. In general, low-risk patients with both metastatic and non-metastatic disease usually respond to single-agent chemotherapy, whereby the most commonly used agents are sequential methotrexate (MTX) and actinomycin D (ACT-D). In case of resistance, several combination regimens can be used, such as the MAC regimen (MTX, ACT-D, and cyclophosphamide) or the EMACO regimen (etoposide, MTX, ACT-D, cyclophosphamide, and vincristine).

The high-risk patients are to be treated from the start with combination chemotherapy; for stages II or III and a FIGO prognostic score ≥7 and stage IV, preferably initially with EMACO; and in case of resistance, with drug combinations including both a platinum agent and etoposide, with or without bleomycin or ifosfamide [86].

Since GTN has a strong expression of PD-L1, suggesting the ligand is involved in tumor–immune evasion, the anti-PD1 antibody, pembrolizumab has been used in patients failing several lines of chemotherapy and showed activity in some of these patients [87].

5.7 Cytotoxic Agents in Gynecologic Cancers

5.7.1 Alkylating Agents

Alkylating agents (Table 5.1) are so named because of their ability to alkylate many nucleophilic functional groups under conditions present in cells. They impair cell function by forming covalent bonds with the amino, carboxyl, sulfhydryl, and phosphate groups in biologically important molecules. The most important sites of alkylation are DNA, RNA, and proteins. The electron-rich nitrogen at the 7 position of guanine in DNA is particularly susceptible to alkylation. The alkylating agents depend on cell proliferation for activity but are not cell cycle phase specific. A fixed percentage of cells are killed at a given dose [88–90].

5.7.2 Antitumor Antibiotics

There are many differing antitumor antibiotics (Table 5.2), but generally they prevent cell division in two ways: (1) binding to DNA, making it unable to separate, and (2) inhibiting ribonucleic acid (RNA), preventing enzyme synthesis [88–90].

5.7.3 Antimetabolites

Antimetabolites (Table 5.3) masquerade as purines (azathioprine, mercaptopurine) or pyrimidines, which become the building blocks of DNA. They prevent these

Table 5.1 Alkylating agents used for gynecologic cancer

Cytotoxic drug	Route of administration	Treatment schedule	Diseases
Cisplatin	IV or IP	10–20 mg/m^2 × 5 every 3 weeks	Ovarian cancer, non-epithelial ovarian cancer, carcinosarcomas endometrial cancer, cervical cancer
		50–75 mg/m^2 every 1–3 weeks	
Carboplatin	IV	AUC 5–AUC 7.5	Ovarian cancer, cervical cancer, endometrial cancer
Dacarbazine	IV	2–4.5 mg/kg/day × 10 every 4 weeks	Sarcomas
Cyclophosphamide	IV or oral	1.5–3.0 mg/kg/day oral	Ovarian cancer, sarcomas
		10–50 mg/kg IV every 1–4 weeks	
Ifosfamide	IV	5 g/m^2	Cervical cancer, sarcomas, carcinosarcomas
Hexamethylmelamine	Oral	260 mg/m^2 14 days/4 weeks	Ovarian cancer

Abbreviations: *IV* intravenously, *IP* intraperitoneally, *AUC* area under the curve

Table 5.2 Antitumor antibiotics used for gynecologic cancer

Cytotoxic drug	Route of administration	Treatment schedule	Treated diseases
Actinomycin D	IV	0.3–0.5 mg/m^2 IV × 5 days every 3–4 weeks	Ovarian germ cell tumors, gestational trophoblastic disease, sarcomas
Bleomycin	IV, SC, IM	30 mg	Cervical cancer, germ cell tumors
Mitomycin C	IV	10–20 mg/m^2 every 6–8 weeks	Cervical cancer
Doxorubicin	IV	60–90 mg/m^2 every 3 weeks or 20–35 mg/m^2 every day × 3 every 3 weeks	Ovarian cancer, endometrial cancer, sarcomas
Doxil/Caelyx (liposomal doxorubicin)	IV	30–50 mg/m^2	Ovarian cancer

Abbreviations: *IV* intravenously, *SC* subcutaneously, *IM* intramuscular

substances from becoming incorporated into DNA during the "S" phase of the cell cycle, stopping normal development and division. They also affect RNA synthesis. Owing to their efficacy, these drugs are the most widely used cytostatic drugs. Antimetabolites have a nonlinear dose–response curve, such that after a certain dose, no more cells are killed despite increasing doses (fluorouracil is an exception) [88–90].

Table 5.3 Antimetabolites used for gynecologic cancer

Cytotoxic drug	Route of administration	Treatment schedule	Treated diseases
5-Fluorouracil	IV	10–15 mg/kg/week	Ovarian cancer, cervical cancer
Methotrexate	IV, oral, intrathecal	240 mg/m^2 IV with leucovorin rescue	Gestational trophoblastic disease, ovarian cancer
		15–40 mg/day oral × 5 days	
		12–15 mg/m^2/week intrathecal	
Hydroxyurea	IV, oral	1–2 mg/m^2 daily for 2–6 weeks	Cervical cancer (only in combination with RT)
Gemcitabine	IV	1000 mg/m^2	Ovarian cancer, cervical cancer

Abbreviation: *IV* intravenously

Table 5.4 Plant alkaloids in gynecologic cancer

Cytotoxic drug	Route of administration	Treatment schedule	Treated diseases
Vinca alkaloids			
Vincristine	IV	0.5–1.4 mg/m^2 (max 2 mg/m^2) every 1–4 weeks	Vincristine: ovarian germ cell tumors, sarcomas, cervical cancer
Vinblastine	IV	5–6 mg/m^2 every 1–2 weeks	Vinblastine: ovarian germ cell tumors, gestational trophoblastic disease
Taxanes			
Paclitaxel	IV	175 mg/m^2 3 weekly or 70–90 mg/m^2 weekly	Paclitaxel: ovarian cancer, cervical cancer, endometrial cancer, sarcomas
Docetaxel	IV	75 mg/m^2 3 weekly	Docetaxel: ovarian cancer, cervical cancer, endometrial cancer, sarcomas
Podophyllotoxins			
Etoposide (VP-16)	IV	300–600 mg/m^2 divided over 3–4 days every 3–4 weeks	Ovarian germ cell tumors, gestational trophoblastic disease

Abbreviation: *IV* intravenously

5.7.4 Plant Alkaloids

Plant alkaloids (Table 5.4) are derived from plants and block cell division by preventing microtubule function. Microtubules are vital for cell division, and, without them, cell division cannot occur. The main examples are vinca alkaloids, taxanes, and podophyllotoxins.

Vinca alkaloids bind to specific sites on tubulin, inhibiting the assembly of tubulin into microtubules (M phase of the cell cycle). They are derived from the Madagascar periwinkle, Catharanthus roseus (formerly known as Vinca rosea).

Table 5.5 Topoisomerase inhibitors in gynecologic cancer

Cytotoxic drug	Route of administration	Treatment schedule	Treated diseases
Type I topoisomerase inhibitors			
Topotecan	IV	1.5 mg/m^2/day for 5 days, 4 weekly	Topotecan: cervical cancer
Type II topoisomerase inhibitors			
Etoposide	IV	300–600 mg/m^2 divided over 3–4 days every 3–4 weeks	Ovarian germ cell tumors, gestational trophoblastic disease

Podophyllotoxin is a plant-derived compound that is said to help with digestion. It is also used to produce two other cytostatic drugs, etoposide and teniposide. They prevent the cell from entering the G1 phase (the start of DNA replication) and the replication of DNA (the S phase).

The prototype taxane is the natural product paclitaxel and first derived from the bark of the Pacific Yew tree. Docetaxel is a semisynthetic analogue of paclitaxel. Taxanes enhance stability of microtubules, preventing the separation of chromosomes during anaphase [88–90].

5.7.5 Topoisomerase Inhibitors

Topoisomerases (Table 5.5) are essential enzymes that maintain the topology of DNA. Inhibition of type I or type II topoisomerases interferes with both transcription and replication of DNA by upsetting proper DNA supercoiling. Type II topoisomerase inhibitor etoposide is extracted from the alkaloids found in the roots of mayapple plants. They work in the late S and G2 phases of the cell cycle. Etoposide's chemical makeup derives from podophyllotoxin, a toxin found in the American mayapple [88–90].

5.7.6 Other Agents

5.7.6.1 Trabectedin

Trabectedin, a marine-derived antineoplastic agent initially isolated from the tunicate Ecteinascidia turbinata, is currently produced synthetically. It binds covalently to the minor groove of DNA, bending DNA toward the major groove, and disrupts transcription, leading to G2-M cell cycle arrest and ultimately apoptosis. Unlike platinum compounds, trabectedin is more cytotoxic in cells with an efficient transcription-coupled nucleotide excision repair system.

Trabectedin is indicated in platinum-sensitive ovarian cancer (recurrence >6 months platinum-free interval) and sarcomas [91, 92].

5.7.6.2 Etirinotecan Pegol (NKTR-102)

Etirinotecan pegol is a next-generation topoisomerase I inhibitor that has been engineered to provide a continuous concentration of active drug with reduced peak

concentrations. It was designed using Nektar's advanced polymer conjugate technology platform and is active in patients with platinum-resistant ovarian cancer [93].

5.7.6.3 Epothilones

Epothilones are a new class of antimicrotubule agents, originally discovered in 1987 from the fermentation of soil bacteria found on the banks of the Zambezi River in Africa.

Their chemical structures are distinct from taxanes, and they are more amenable to synthetic modification.

Epothilones are microtubule-stabilizing agents that inhibit cell growth. They bind to the β-tubulin subunit of the αβ-tubulin dimer of microtubules and induce microtubule polymerization and stabilization, resulting in G2/M arrest and the induction of apoptosis. Epothilones are less susceptible than taxanes to overexpression of P-glycoprotein, the presence of certain tubulin isoforms (class III β-tubulin), and tubulin mutations, all of which have been implicated in taxane resistance. Although epothilones share a similar mechanism of action with the taxanes, they are structurally unrelated.

Six epothilones have been studied in preclinical and clinical trials: patupilone (epothilone B), ixabepilone (BMS247550), BMS 310705, sagopilone (ZK-EPO), KOS-862 (epothilone D), and KOS-1584. In vitro data have shown increased potency in taxane-sensitive and taxane-resistant cancer cell lines [88, 89].

Responses to epothilones have been observed in platinum-refractory/resistant ovarian cancer patients [94].

5.8 Side Effects of Systemic Therapy: Prevention and Treatment

Antineoplastic drugs are among the most toxic agents used in modern medicine. In the first-line setting, chemotherapy is often used with curative intent. Once the disease recurs locoregionally or at distant site, many times the main goal of cytotoxic treatment is the relief of disease-related symptoms and prolongation of PFS and overall survival while maintaining QoL as much as possible.

Many of the side effects, particularly those to organ systems with a rapidly proliferating cell population, are dose related and predictable. In almost all instances, chemotherapeutic agents are used in doses that produce some degree of toxicity to normal tissues.

Severe systemic debility, advanced age, poor nutritional status, or direct organ involvement by primary or metastatic tumor can result in unexpected severe side effects of chemotherapy.

At each stage of the disease, careful monitoring and assessment of benefit versus harm in each individual patient is a major responsibility of the physician dealing with cytotoxic agents [95, 96].

The commonly used agents in gynecologic cancer, their main side effects, and their prevention and management are described in the next sections.

5.8.1 Chemotherapy

5.8.1.1 Platinum Agents

Platinum agents used in gynecologic cancer include cisplatin and carboplatin [95, 96].

Platinum-based therapy plays an integral role in the first-line treatment as well as in the recurrent disease setting in several gynecologic cancers.

Cisplatin is associated with several cumulative toxicities [88], including dose-dependent renal tubule toxicity and neurotoxicity.

Extensive renal damage can occur before any detectable changes in serum creatinine levels [97]. Renal impairment can lead to a reduction in the clearance of some co-administered cytotoxic agents and may potentially increase severe toxicities. Vigorous hydration with adequate diuresis is necessary during cisplatin administration to minimize the risk and severity of acute nephrotoxicity [96].

Amifostine, a naturally occurring thiol that can protect cells from damage by scavenging oxygen-derived free radicals, may be considered for the prevention of nephrotoxicity in patients receiving cisplatin-based chemotherapy [96].

Peripheral neuropathy, ototoxicity, and rarely retrobulbar neuritis and blindness are known side effects of cisplatin. High doses of cisplatin are particularly likely to produce a progressive and delayed peripheral neuropathy. This defect is characterized by sensory impairment and loss of proprioception, where motor strength generally is preserved. Progression of this neuropathy 1–2 months after cessation of high-dose cisplatin has been reported. Diagnosis of neuropathy is typically based on patient history, physical examination, and if necessary an electromyography. Permanent high-tone hearing loss can occur in up to 45% of patients receiving cisplatin therapy [96].

There has been lack of good evidence for the routine use of neuroprotective agents such as vitamin E, amifostine, amitriptyline, gabapentin, and other agents. Few treatment options for neuropathic pain are described, but those are not validated by large, randomized controlled trials. In small numbers of patients, gabapentin, 400 mg three times daily, and amitriptyline, 10–50 mg, have been shown to provide relief in severe neuropathic pain [96].

Hypersensitivity reaction resulting in rash, bronchospasm, urticaria, and hypotension increases with continued use of cisplatin. Prophylactic treatment with steroids and antihistamines and a slow infusion rate may minimize this risk [96].

Gastrointestinal adverse events are also common with cisplatin therapy and may be acute or delayed in onset. Nausea and vomiting are the major complaints among cisplatin-treated patients. Use of 5-hydroxytryptamine-3 inhibitors (e.g., granisetron, ondansetron, tropisetron, palonosetron) in combination with corticosteroids and NK-1 receptor antagonists (e.g., (fos)aprepitant, netupitant) can reduce the incidence and severity of these effects [98].

Myelosuppression with leukopenia and anemia occurs in nearly half of cisplatin-treated patients with advanced ovarian cancer. Despite relatively high rates of low neutrophil counts when cisplatin is used, the rate of febrile neutropenia is low, especially when used in monotherapy. Treatment with hematopoietic growth factors

such as granulocyte colony-stimulating factor (G-CSF) can be useful in some cases. The use of G-CSF for primary prophylaxis is only indicated in regimens with a risk of febrile neutropenia of 20% (e.g., cisplatin/paclitaxel). The use of G-CSF for the treatment of febrile neutropenia is not recommended, except in settings with increased morbidity and mortality, including sepsis, tissue infection, and prolonged neutropenia [99].

Anemia can lead to many symptoms, including fatigue, subsequently impacting on patients' activities of daily living. The role of the erythropoietin-stimulating agents (ESAs) continues to be investigated. US FDA labeling for ESAs contains a black box warning of adverse effects on survival, progression, and recurrence. Concerns regarding ESA use in a curative setting have been raised, but its use may be appropriate for patients in whom therapy is palliative [100].

The cumulative and irreversible toxicities associated with cisplatin may reduce the potential options for future treatment on relapse. Many new platinum-based formulations have been derived to minimize the severe toxicity profiles associated with cisplatin treatment. These compounds include carboplatin, which is approved for use in ovarian cancer, oxaliplatin, nedaplatin, satraplatin, and other investigational drugs [101].

Carboplatin is an alternative for platinum therapy that exhibits considerably lower nephrotoxicity than cisplatin. However, renal function must be monitored when determining dosage regimens to avoid acute toxicity because the renal clearance is the primary means by which carboplatin is cleared from the body. Carboplatin can cause dose-limiting and cumulative myelosuppression. Thrombocytopenia is frequent and severe, and thrombocyte transfusions can be necessary. Other side effects of carboplatin administration are neurotoxicity and hypersensitivity reactions. Hypersensitivity to carboplatin was seen in 12% of carboplatin-treated patients in a study conducted by [101]. Because of the possibility of fatal cross-hypersensitivity, the use of cisplatin in patients who have developed hypersensitivity to carboplatin is not recommended [102, 103].

Attempts are made to improve outcome in terms of PFS and quality of life in ovarian cancer patients by modifying scheduling and dose-density of systemic treatment.

A phase III randomized, controlled trial of conventional TC treatment (carboplatin AUC 6 and paclitaxel 180 mg/m^2, 3 weekly) versus dose-dense treatment (carboplatin AUC 6, 3 weekly and paclitaxel 80 mg/m^2, weekly) in 637 patients with a median follow-up of 76.8 months showed a superior PFS (28.2 vs. 17.5 months) and overall survival (100.5 vs. 62.2 months) in the advantage of the dose-dense arm [13, 104].

QoL outcome analysis showed that the dose-dense regimen does not decrease overall QoL. The overall QoL did not differ significantly between the two treatment groups up to 12 months after randomization [104].

The MITO 7 trial compared a standard 3-weekly TC regimen with weekly carboplatin (AUC 2) and weekly paclitaxel (60 mg/m^2), achieving comparable PFS with improved tolerability on the weekly regimen. The lack of superiority associated with the weekly regimen is most likely related to fractionation of carboplatin, rather than the lower dose of weekly paclitaxel [104].

A phase II study of weekly paclitaxel (60 mg/m^2)/carboplatin (AUC 2.7) in combination with prophylactic G-CSF in the treatment of 108 patients with gynecologic cancers (recurrent platinum-resistant ovarian cancer, recurrent or advanced endometrial cancer or cervical cancer) showed efficacy and feasibility of this regimen. The incidence of grade 3–4 neutropenia was lower with the addition of weekly G-CSF compared with earlier studies without routine use of prophylactic G-CSF [105].

Platinum agents (i.e., cisplatin and carboplatin) are the drugs of preference for the treatment of concomitant chemoradiotherapy in cervical cancer. The treatment of choice is cisplatin, 40 mg/m^2, administered weekly. Despite the fact that weekly cisplatin during radiation is well tolerated, its nephrotoxicity is of particular concern in a patient population that frequently has renal dysfunction as a consequence of ureteral obstruction by the disease spreading to the pelvic wall or to the bladder. Carboplatin has fewer side effects than cisplatin with significantly less gastrointestinal, neural, and renal toxicity. The activity of carboplatin given concurrently with radiotherapy for cervical cancer has been reported and is attractive, especially in terms of toxicity [106].

A particular advantage of concurrent chemotherapy with radiation is the enhancement effect on radiation, leading to better locoregional control, but an early effect on micrometastases might be an additional effect. It has been shown that this cisplatin-based chemoradiation reduces the treatment failures compared to radiotherapy alone and improves cervical cancer survival by approximately 40% [107–109]. Patients are, however, likely to experience additive toxicities as a result of this combined treatment, and acute toxicities (e.g., hematologic toxicity, nausea, vomiting) are more common with chemoradiation than with radiation alone. Acute gastrointestinal symptoms typically involve varying degrees of diarrhea, abdominal discomfort, cramping, nausea, and vomiting. High-risk factors associated with radiotherapy complications are obesity, smoking, pelvic inflammatory disease, diverticulosis, treatment field, and dose [110].

Late toxicities include small bowel obstruction secondary to radiotherapy fibrosis, radiotherapy-induced hemorrhagic cystitis, urinary retention secondary to urethral stricture, complex fistulas, and radiotherapy enteritis and pancreatitis. Some of these late toxicities necessitate surgical intervention [110].

Chronic gastrointestinal toxicity usually occurs in the first 2 years after treatment in about 10% of patients, with an average interval ranging from 6 to 18 months [111]. Acute gastrointestinal side effects such as diarrhea and fecal incontinence may become chronic. Acute toxicity is usually reversible, and most acute adverse events are self-limiting or resolve with medical management (hydration, loperamide, analgesics), while late effects are often permanent and affect the QoL [112].

5.8.1.2 Taxanes

Taxanes include paclitaxel and docetaxel.

Paclitaxel is a non-platinum-based cytotoxic agent approved for the first-line treatment of advanced ovarian cancer with high antitumor activity when used in combination with carboplatin (PC regimen). Also, in recurrent platinum-sensitive disease, this PC regimen seems to improve PFS and overall survival [4].

Carboplatin could be safely combined with paclitaxel using a dose formula based on projected renal clearance. The recommended outpatient regimen is carboplatin AUC 7.5 and paclitaxel 175 mg/m^2 over 3 h without initial G-CSF. However, the use of paclitaxel may be limited by cumulative peripheral neurotoxicity, and a rapid-onset sensory neuropathy can occur. The peripheral neuropathy is due to axonopathy, and also the motor and autonomic nerves appear to be affected by paclitaxel. In this case, docetaxel can be an alternative for paclitaxel, since neurotoxicity is uncommon in the combination of carboplatin/docetaxel [113, 114].

Docetaxel has been examined in several clinical trials for management of platinum-resistant and sensitive ovarian cancer, with an objective response rate of approximately 20–35% being documented in this clinical setting. This level of activity is comparable to that of paclitaxel observed in a similar patient population.

The dose of single-agent docetaxel in these studies has been 100 mg/m^2, delivered on an every 3 weeks schedule. It is not known if a lower-dose regimen (e.g., 60 or 80 mg/m^2) might result in similar response rates with reduced toxicity. The drug is generally well tolerated in this setting, with the major toxicity being neutropenia and a capillary leak syndrome with fluid accumulation that is related to the cumulative dose and number of cycles.

The toxicities caused by docetaxel use are more pronounced in patients with elevated liver function tests (i.e., transaminase levels greater than 1.5 times the upper limit of normal and alkaline phosphatase levels greater than 2.5 times the upper limit of normal) [105].

The comparison of docetaxel/carboplatin with the standard PC regimen has been studied in the SCOTROC trial, the Scottish Randomized Trial in Ovarian Cancer (paclitaxel 175 mg/m^2 administered for 3 h or docetaxel 75 mg/m^2 administered for 1 h in combination with carboplatin AUC 5), given for six cycles every 21 days. The main differences in toxicity between the two regimens are related to neurotoxicity and myelosuppression, with more neurotoxicity seen with the PC regimen and more myelosuppression seen in the docetaxel plus carboplatin combination [115, 116].

Arthralgias and myalgias are well-described toxicities associated with taxanes and can be very painful and at times disabling. The natural history is to improve with each course of treatment [117]. Arthralgias/myalgias are often difficult to treat, and many patients do not respond to simple analgesics. In a phase II study reported by Markman et al., 46 patients with unacceptable myalgias and arthralgias, despite the use of nonsteroidal anti-inflammatory drugs, were treated with 10-mg twice-daily oral prednisone for 6 days. They reported that 85% of patients experienced relief of myalgias and arthralgias [118]. Savarese et al. described a pilot study of five patients treated with oral glutamine 10 g three times a day in patients who had developed severe myalgias or arthralgias with their first cycle of paclitaxel. They reported that on glutamine there were no myalgias or arthralgias reported [119].

The acute dose-limiting toxicity of taxanes is the granulocytopenia. Other common side effects include alopecia, nausea, vomiting, diarrhea, mucositis, and hypersensitivity. To decrease the incidence and severity of hypersensitivity reactions, patients should receive pretreatment with steroids. In case of treatment with paclitaxel, the use of a H1 (e.g., promethazine, diphenhydramine) and H2 (e.g.,

cimetidine, ranitidine) receptor antagonist besides corticosteroids is recommended one-half hour before the administration of paclitaxel [120]. Moreover, concomitant steroid therapy allows paclitaxel to be administered over a 3-h infusion period, which is less myelosuppressive than the 24-h infusion [121, 122].

Rarely, acute pneumonitis, as well as an isolated case of fatal pulmonary fibrosis, has been seen with paclitaxel use. Close monitoring of patients with underlying pulmonary disease is mandatory, and if pneumonitis develops, treatment with steroids is appropriate [123].

5.8.1.3 Topotecan

Topotecan has efficacy in advanced ovarian cancer that is comparable with that of both paclitaxel and liposomal doxorubicin. Compared with paclitaxel and liposomal doxorubicin, the majority of topotecan's serious side effects are short-lived, reversible, and noncumulative [124]. The traditional dose schedule is 1.5 mg/m^2/day × 5 every 3 weeks, but more convenient weekly regimens are used also [125, 126].

A randomized phase III study (GOG-0240) which compared the addition of bevacizumab to paclitaxel plus cisplatin or paclitaxel plus topotecan led to a higher incidence of grade 2 or higher hypertension (25% vs. 2%), grade 3 or higher thromboembolic events (8% vs. 1%), and grade 3 or higher gastrointestinal fistulas (3% vs. 0%) [64].The most important adverse effect seen in all patients was myelosuppression. Grade 4 neutropenia was observed in 79% of topotecan patients receiving second-line therapy and in 81% of the patients who received third-line therapy. The highest incidence of grade 4 neutropenia was observed during the first course (57% of all patients during second-line treatment and 59.3% during third-line treatment), and this decreased in subsequent courses. Grade 4 thrombocytopenia was also higher in patients who received topotecan in both second-line and third-line treatment regimens. In the topotecan-treated group, myelosuppression was noncumulative, manageable, and resolved quickly (nadir 5–7 days). For the topotecan group, non-hematologic toxicity consisting primarily of gastrointestinal disturbances (nausea, vomiting, stomatitis, diarrhea, constipation) was generally mild or moderate (grade 1/2). Alopecia is the only cumulative toxicity reported during long-term topotecan therapy.

No end-organ toxicities, such as cardiac, neurologic, skin, or ototoxicity, were observed, and all non-hematologic toxicities were noncumulative [127].

Topotecan is not associated with significant nephrotoxicity. However, prior treatments might have compromised renal function, and because this may influence the renal clearance of topotecan (which correlates with the creatinine clearance), leading to more myelosuppression, assessment of the kidney function before the treatment with topotecan starts is essential. Also dose/schedule adjustments should be based on the patient's treatment history with cytotoxic agents that have cumulative myelotoxicity (e.g., carboplatin) as well as the use of extensive prior radiotherapy [128]. Dose reductions have not shown to decrease response rates. Reducing the starting dose to 1.0 or 1.25 mg/m^2/day × 5 is recommended, and this may reduce the incidence of severe myelosuppression in such patients [129]. Hematopoietic growth factors, transfusion therapy, and schedule adjustments may also help manage

myelosuppression [130]. Although the liver also contributes to the clearance of topotecan, no dose modifications are necessary in patients with impaired hepatic function [131]. As the thrombopenic effect of topotecan decreases with each next treatment cycle, even in patients who have been heavily pretreated, long-term use of topotecan as palliative therapy for the advanced ovarian cancer is feasible [132].

5.8.1.4 Gemcitabine

Gemcitabine is used in combination with carboplatin in recurrent ovarian cancer [133]. Also, as a single agent in second-line treatment for advanced ovarian cancer, it is found to offer benefit. The response rates with single-agent gemcitabine range from 13% to 24%, both in previously treated and untreated patients [134]. Doublets consisting of gemcitabine-cisplatin or gemcitabine-paclitaxel, in previously treated patients, induce responses in 53% and 40% of the patients, respectively. Triplet combinations have also shown to be effective in early-stage trials, although dose-limiting myelosuppression occurs with gemcitabine plus paclitaxel plus carboplatin [135, 136].

Myelosuppression is the primary dose-limiting toxicity of gemcitabine, especially when given in combination with cisplatin or carboplatin because of their overlapping toxicity. Frequent monitoring of hematologic parameters and application of dose modifications, if needed to manage the anemia, leukopenia, and thrombocytopenia, are recommended [137, 138].

Other common adverse events are flu-like symptoms (e.g., fever, rigors, and malaise) and lethargia [139].

Less common is dyspnea, which must be distinguished from the symptoms of drug-induced pneumonitis and non-cardiogenic pulmonary edema (NCPE), which are rare but life-threatening adverse events. Although the effects of NCPE are usually reversible with immediate intensive supportive therapy, gemcitabine should be stopped at the first sign of this complication [140, 141].

Other side effects of gemcitabine include grade 3 vomiting, manageable fever, peripheral edema, and alopecia; no cumulative hepatic or direct renal toxicities have been reported [142, 143].

After extended gemcitabine use, the development of thrombotic microangiopathy and a life-threatening hemolytic uremic syndrome can occur [144].

5.8.1.5 Oral Etoposide

Etoposide is active in malignant ovarian germ cell tumors and gestational trophoblastic neoplasms. The commonly used chemotherapy regimen in these tumor types is bleomycin, etoposide, and cisplatin (BEP) [145].

The activity of prolonged oral administration of etoposide in second-line therapy for advanced ovarian cancer has been studied in a phase II trial by Rose et al. (GOG Group study). The same author studied this regimen in advanced recurrent leiomyosarcoma of the uterus and recurrent or advanced squamous cell carcinoma of the cervix but without success. In cervical cancer, prior radiation therapy limited the ability to deliver prolonged oral etoposide due to hematologic toxicity with grade 4 neutropenia and thrombocytopenia occurring in, respectively, 33.3% and 15% of the patients [146–148].

Prolonged oral use of etoposide and higher cumulative doses in EOC have shown that there is an increased risk of developing secondary myelodysplasia and acute leukemias; therefore, this agent is mostly not used in the primary treatment setting. Severe hematologic toxicities are common during long-term etoposide therapy. Grade 3/4 neutropenia and leukopenia occur in 45% and 41% of etoposide-treated patients, respectively. Deaths from neutropenic sepsis have been reported. Thrombocytopenia and anemia occur at a lower incidence compared with neutropenia and leukopenia. Myelosuppression from etoposide is generally reversible with no cumulative bone marrow toxicity [148]. Regular blood count and support with hematopoietic growth factors will be useful.

Other manageable side effects are alopecia, nausea, vomiting, anaphylaxis, mucositis, and acute hypo- and hypertensive responses [149].

5.8.1.6 Anthracyclines

Anthracyclines used in gynecologic cancers include doxorubicin and pegylated liposomal doxorubicin (PLD).

Doxorubicin is known to be an active agent in endometrial cancer and EOC, and it is often combined with a platinum compound [150–152]. Unfortunately, the clinical use of doxorubicin is limited by its dose-related cardiomyopathy, which becomes more prevalent with increasing cumulative doses. Doxorubicin therapy can be associated with irreversible cardiotoxicity, which may manifest as life-threatening arrhythmias during the acute phase of treatment and leads to a high risk of congestive heart failure [153].

PLD is a formulation of doxorubicin encapsulated in polyethylene glycol (PEG)-coated liposomes associated with a dramatic alteration in pharmacokinetics characterized by a prolonged circulation time and a small volume of distribution. Liposomes can eventually extravasate through abnormally permeable vessels, which are frequently associated with tumors, and can theoretically deliver high local levels of doxorubicin [154].

PLD is approved for the treatment of advanced ovarian cancer in women refractory to both platinum- and paclitaxel-based chemotherapy regimens. It has comparable efficacy with other second-line or salvage regimens and conventional doxorubicin but has a more favorable toxicity profile [155].

PLD is associated with a dose-limiting hand-foot syndrome (or palmar-plantar erythrodysesthesia syndrome) characterized by painful erythema, peeling, and occasional blistering, which can generally be managed by prolongation of the treatment interval to 4 weeks and/or dose reduction and ultimately drug withdrawal. Almost 50% of all patients receiving PLD experience hand-foot syndrome (grade 3/4 in 23% of the patients). There is no established pharmacologic treatment for the hand-foot syndrome, and the use of ointments and behavior modification to prevent cracking of the skin can help to improve the pain [156].

The risk of cardiomyopathy with PLD is reduced compared to free doxorubicin. Histologic examination of cardiac biopsies from patients who received cumulative doses of PLD from 440 to 840 mg/m^2, without prior anthracycline exposure, revealed significantly less cardiac toxicity than in matched doxorubicin controls. However, the cumulative cardiotoxicity of the liposomal formulation has not been

established; therefore, extended use of liposomal doxorubicin in patients with impaired myocardial function is contraindicated [156].

Other side effects of PLD are mucositis, hematologic toxicity, alopecia, acute nausea, and vomiting, all of which are manageable. In a phase III trial comparing carboplatin/PLD versus the standard PC regimen in patients with platinum-sensitive recurrent EOC, the combination with carboplatin/PLD was superior in terms of PFS and showed a better therapeutic index [157].

5.8.1.7 Vincristine/Vinblastine

Vinca alkaloids are mainly used in ovarian germ cell tumors (OGCT). The first effective combination chemotherapy for patients with OGCT was the VAC regimen (vincristine, actinomycin D, and cyclophosphamide). Since a remarkable improvement of survival in male testicular cancer patients treated with PVB polychemotherapy (cisplatin, vinblastine, and bleomycin), this regimen was also introduced in OGCT. The PVB regimen proved to be active and more effective than the VAC regimen [157].

Despite the fact that there is only a small structural difference between vincristine and vinblastine, they have significantly different antitumor spectrums and toxicity patterns. Vinblastine has myelosuppression as its primary toxicity, whereas the dose-limiting toxicity for vincristine is the peripheral neuropathy. Toxicity first appears as loss of deep tendon reflexes with distal paresthesia. Cranial nerves can be affected, and the autonomic neuropathy can appear as a dynamic ileus, urinary bladder atony with retention, or hypotension. Older patients and patients who already have neuropathic symptoms due to diabetes mellitus, hereditary neuropathies, or earlier treatment with neurotoxic chemotherapy are thought to be more vulnerable for the development of chemotherapy-induced peripheral neuropathy. Vincristine-induced neuropathy usually starts after a cumulative dose of 5- to 6-mg vincristine (but autonomic neuropathy in particular can occur even after the first administration), and nearly all patients experience some degree of neuropathic signs or symptoms.

Management mainly consists of (cumulative) dose reduction or lower-dose intensities, especially in patients who have a higher risk of developing neurotoxic side effects. Neuroprotective agents should ideally protect the nervous system without affecting the antitumor effect of the cytostatic agent. For many years now, potential neuroprotective agents (e.g., nerve growth factor, glutamine, amifostine, glutamate, and vitamin E) have been studied, with different results. However, none of these agents can be recommended for standard use in daily clinical practice. Vincristine-induced neuropathy may persist for up to 40 months but in general has a good prognosis [158–160].

5.8.1.8 Ifosfamide

Ifosfamide is an alkylating agents. In gynecologic cancer, mostly it is used in association with cisplatin. In second-line therapy for ovarian cancer, it shows remarkable activity, even in patients refractory to cisplatin, with more severe, but always manageable toxicity [161].

In gynecologic sarcomas, ifosfamide is, together with doxorubicin, an important component in the regimen [162, 163]. The combination of cisplatin, ifosfamide, and doxorubicin (PIA) proved to be very active but too toxic.

The TIP (paclitaxel, ifosfamide, and cisplatin) regimen is highly active (with response rates of 48%) in locally advanced and relapsed/metastatic cervical cancer, although hematologic toxicity associated with this treatment is considerable and supportive measures (hematopoietic growth factors) are needed [164, 165].

The dose-limiting toxicities of ifosfamide are myelosuppression (especially leukopenia) and hemorrhagic cystitis. Hemorrhagic cystitis is a diffuse inflammation of the bladder leading to dysuria, hematuria, and hemorrhage. Acrolein, a metabolite of ifosfamide and cyclophosphamide, is the main molecule responsible of this side effect. Hemorrhagic cystitis can be prevented by the use of aggressive hydration and the use of mesna (2-mercaptoethanesulfonic acid), which neutralizes the toxicity of the acrolein. Mesna binds acrolein and prevents its direct contact with uro-epithelium [166].

Other side effects are nausea, vomiting, alopecia, neurologic disorders, and elevated serum creatinine levels. Neurologic symptoms include episodes of somnolence, lethargy, ataxia, disorientation, confusion, dizziness, malaise, depressive psychosis, and coma. These toxicities occur more frequently when ifosfamide is given over a 1-day period instead of 5 days. A total of 10–15% of patients treated with ifosfamide develop an encephalopathy. The exact pathophysiologic mechanisms responsible for the development of ifosfamide-induced encephalopathy are not known. However, accumulation of chloroacetaldehyde, toxic metabolite of ifosfamide, in the central nervous system is theorized to be the cause of the neurotoxicity. The intravenous use of methylene blue in a dosage of 6×50 mg/day for treatment and 4×50 mg/day, either intravenously or orally, for secondary prophylaxis of ifosfamide-induced encephalopathy is recommended [167].

Syndrome of inappropriate antidiuretic hormone secretion (SIADH) is characterized by hyponatremia and high urinary osmolality (>100 mOsm/kg) due to inappropriately high serum levels of arginine vasopressin in a clinically euvolemic patient. Hypouricemia urinary sodium level >40 mEq/L and low blood urea nitrogen (BUN) may also indicate diagnosis of SIADH. SIADH affects 1–2% of all cancer patients and accounts for 30% of hyponatremia in this population. Ifosfamide has been reported as a cause of SIADH. Hypertonic saline, loop diuretics, fluid restriction, and demeclocycline are mainstays of therapy for SIADH [168–170].

5.8.1.9 Cyclophosphamide

Cyclophosphamide can be successfully used in ovarian cancer, soft-tissue sarcoma, and granulosa cell tumor. In ovarian cancer, the preferred regimen is the association with cisplatin. However, this regimen is less effective compared with the currently used PC standard regimen [171]. In soft-tissue sarcoma and granulosa cell tumors, it is preferably combined with Adriamycin and cisplatin [172, 173].

Side effects of cyclophosphamide include chemotherapy-induced nausea and vomiting, bone marrow suppression, epigastric pain, diarrhea, darkening of the skin/nails, alopecia (hair loss) or thinning of hair, changes in color and texture of

the hair, and lethargy. Hemorrhagic cystitis is a frequent complication in case of high dosage regimens that can be adequately prevented by sufficient fluid intake and mesna.

Cyclophosphamide is itself carcinogenic, potentially causing transitional cell carcinoma of the bladder as a long-term complication. Another serious side effect is acute myeloid leukemia (AML), referred to as secondary AML. The risk of its development may be dependent on dose and a number of other factors, including the condition being treated, other agents or treatment modalities used (including radiotherapy), treatment intensity, and length of treatment. Cyclophosphamide-induced AML, when it happens, typically presents some years after treatment, with incidence peaking around 3–9 years. After 9 years, the risk has fallen to the level of the regular population. When AML occurs, it is often preceded by a myelodysplastic syndrome phase, before developing into overt acute leukemia. Cyclophosphamide-induced leukemia will often involve complex cytogenetics, which carries a worse prognosis than the de novo AML [174, 175].

5.8.1.10 Bleomycin

Bleomycin, first isolated in 1966 by Umazawa and associates, is a cytotoxic antibiotic synthesized from Streptomyces verticillus. It is used primarily in the therapy of lymphomas, squamous cell carcinomas, and germ cell tumors and has little myelosuppressive or immunosuppressive activity.

Bleomycin, etoposide, and cisplatin (BEP) regimen is a modified PVB regimen by substitution of etoposide for vinblastine in ovarian germ cell tumors (OGCT), since the BEP regimen proved to be equally active but less toxic [176].

Bleomycin is an attractive addition to combination chemotherapy regimens because of its broad activity and low myelotoxicity. However, pulmonary toxicity is the major complication limiting its use. Bleomycin is inactivated by a hydrolase enzyme that is relatively deficient in lung tissue. This probably contributes to the sensitivity of lung tissue to the effects of bleomycin. Pulmonary toxicity can present either as an interstitial pneumonitis with progressive fibrosis or, rarely, as an acute hypersensitivity reaction. In both syndromes, the most common symptoms are dyspnea and a nonproductive cough. On examination of the chest, basal crepitations may be present, but often there are few abnormal physical signs. The hypersensitivity reaction may be associated with fever and eosinophilia. Several factors may contribute to the risk of development of bleomycin pulmonary damage. Above a total dose of 450–500 mg, the incidence of interstitial fibrosis rises from 35% to 40%, and this is associated with a higher mortality. However, cases of pulmonary toxicity have been described in patients who have received less than 200 mg. The hypersensitivity reaction is not dose-dependent. Concurrent or previous radiotherapy or therapy with other chemotherapeutic agents, especially cyclophosphamide, and oxygen therapy during or up to 6 months after the administration of bleomycin are additional risk factors. Renal failure may result in higher bleomycin serum levels. Concomitant cisplatin toxicity may contribute to the development of renal failure. Bleomycin should not be given to patients with creatinine clearances <30 mL/min because of the altered pharmacology of the drug in that situation.

There are some reports of symptomatic and radiographic improvement with corticosteroid therapy, especially in the acute situation. However, no controlled studies have been performed to test the role of steroids in treatment. In patients who seemed to improve on steroid therapy, the pulmonary function tests remained abnormal. As treatment of the progressive pulmonary involvement appears relatively unsuccessful, the emphasis should be placed on prevention. All patients who receive bleomycin should have serial pulmonary function tests. If any of the aforementioned risk factors are present, a high index of suspicion should be maintained. It is recommended that further bleomycin therapy should be withheld if the DLCO falls below 40% of the initial value, the FVC decreases by 20%, or if any symptoms, signs, or chest radiograph features of toxicity appear [176–180].

5.8.1.11 Methotrexate

Single-agent methotrexate (MTX) is the first choice for the treatment of low-risk GTN. However, actinomycin D (ACT-D) can be used as a first-line agent in patients with hepatic dysfunction or who have a known adverse reaction to MTX [181]. In case of disease resistant to single agents, the preferred combination chemotherapy regimen is often MAC (MTX, ACT-D, and cyclophosphamide) or EMACO (etoposide, MTX, ACT-D, cyclophosphamide, and vincristine). MAC is preferred as the initial combination chemotherapy regimen since etoposide, which is a component of EMACO, is associated with an increased risk for secondary malignancies. Studies have shown that patients treated with more than 2 g/m^2 of etoposide had a relative risk of 16.6 for developing leukemia, 5.8 for breast cancer, 4.6 for colon cancer, and 3.4 for melanoma [182].

The most described side effects of MTX are mucositis (20–60% rates) with mucosal ulcerations, myelosuppression, hepatotoxicity, allergic pneumonitis, and, in case of intrathecal use, meningeal irritation. High-dose MTX for doses ≥500 mg/m^2 is used in hematologic settings. These regimens deliver an otherwise lethal dose of MTX in a 4- to 36-h infusion, followed by a 2- to 3-day period of multiple leucovorin doses to terminate the toxic effect of MTX (leucovorin "rescue"). Successful rescue by leucovorin depends on rapid elimination of MTX by the kidneys, which requires aggressive pretreatment as well as posttreatment hydration and urinary alkalinization. The main toxicities of high-dose MTX are elevated serum transaminase levels and renal insufficiency, which can delay drug clearance. Doses between 50 and 500 mg/m^2, as used for malignant gestational trophoblastic disease, are considered intermediate-dose MTX. In general, these patients do not require aggressive hydration or urinary alkalinization. Leucovorin rescue is rarely needed with doses ≤250 mg/m^2 unless unexpected toxicity is encountered. When there is renal impairment, leucovorin should be repeated every 6 h until the serum level of MTX falls below 0.1 mmol/L. Alkalinization of urine helps in the excretion of MTX, as MTX and its metabolites are poorly soluble in acidic pH. An increase in the pH of urine from 6.0 to 7.0 increases the solubility of MTX and its metabolites by five to eight times. Aggressive hydration also helps with the renal excretion of MTX and its metabolites [183]. Attention has to be kept on concomitant medication, since many agents are known to prolong MTX elimination, including probenecid, salicylates, nonsteroidal anti-inflammatory drugs (NSAIDs), and weak organic acids [183, 184].

5.8.1.12 5-Fluorouracil

The use of 5-fluorouracil (5-FU) has been studied in recurrent ovarian and cervical cancer, both in phase II trials [185, 186]. In both trials, the main side effects were myelosuppression and gastrointestinal toxicity.

The toxicity of 5-FU, which includes leukopenia, diarrhea, stomatitis, nausea, vomiting, and alopecia, differs with its schedule of administration. Dose-limiting toxicities of bolus 5-FU are diarrhea and myelosuppression. Hand-foot syndrome and stomatitis are also dose limiting with prolonged infusion. Coronary events induced by 5-FU are rare, but considering the potentially lethal nature of this toxicity, physicians should be aware of this possible side effect [187]. Overall, toxicities associated with fluorouracil are more common and more severe in patients with dihydropyrimidine dehydrogenase (DPD) deficiency. Individuals with complete or partial DPD deficiency have a strongly reduced capacity to metabolize 5-FU and therefore experience severe, and sometimes life-threatening, toxic effects from the increased levels of active drug. However, the screening of patients for the presence of DPD deficiency prior to the start of treatment with fluoropyrimidines is not routinely recommended [188].

Numerous approaches have been suggested for managing toxicities caused by 5-FU. The most obvious action would be to stop any further administration of 5-FU in case of severe gastrointestinal toxicity, this followed by aggressive supportive care. Antibiotic and antibacterial coverage may be used in treating potential bacterial and fungal infections resulting from the invasion of enteric organisms through the weakened gut lining. Dehydration and hypotension may be treated with appropriate fluid and electrolyte support. In the most severe cases, hospitalization in the intensive care unit may be necessary.

In case of mucositis, general approaches include effective oral care, dietary modifications, topical mucosal protectants (e.g., Caphosol), topical anesthetics, and systemic analgesics, if necessary. Chlorhexidine oral rinses, as a topical antimicrobial, may be an option to consider when treating an oral infection. Palifermin (keratinocyte growth factor-1) given intravenously has been studied in solid tumor cohorts but is currently not standard of care. One study suggested that palifermin may be useful in a dose of 40 μg/kg/day for 3 days for prevention of oral mucositis in patients receiving bolus 5-FU plus leucovorin.

Oral cryotherapy is recommended for prevention of oral mucositis in patients receiving bolus 5-FU chemotherapy [189].

5.8.1.13 Trabectedin

Trabectedin is indicated in platinum-sensitive ovarian cancer and sarcomas. Its main dose-limiting toxicity is hepatotoxicity and myelosuppression. Premedication with dexamethasone can strongly reduce drug-induced hepatotoxicity and myelosuppression [190]. In a phase II trial in relapsed platinum-sensitive ovarian cancer patients, both every-3-weeks trabectedin regimens, 1.5 mg/m^2 24 h and 1.3 mg/m^2 3 h, were active and reasonably well tolerated. The most common trabectedin-related adverse events were nausea, vomiting, and fatigue, most of them being grade 2 or 3, which were transient, noncumulative, and usually without clinical relevance [191].

However, apart from the advantage of a shorter infusion time, a slightly better safety profile was found for the 3-h schedule with respect to myelosuppression (neutropenia), fatigue, and vomiting. For management of myelosuppression and nausea/vomiting, see previous section. The combination of PLD plus trabectedin (using the 3-h every-3-weeks regimen) has been evaluated versus PLD alone in patients with relapsed EOC. The results of this phase III trial have shown a statistically significant and clinically relevant patient benefit when trabectedin is combined with PLD [192].

5.8.1.14 Etirinotecan Pegol (NKTR-102)

Etirinotecan pegol has been studied in an open-label, phase II trial in a patient population with advanced platinum-refractory ovarian cancer (platinum-free interval <6 months). Median lines of prior therapy for women enrolled in the study were three, with 47% of the women having failed prior treatment with pegylated liposomal doxorubicin. Etirinotecan pegol was given either on a q14d or q21d regimen. Response rates were high, irrespective of the number of lines of prior therapy. Based on this highly promising data set, a phase III study is underway [93].

The most common grade 3 and 4 side effects were diarrhea, dehydration, hypokalemia, fatigue, nausea, and neutropenia, with most side effects being grade 3 in severity; all were manageable with supportive care. One patient in each dose regimen died due to neutropenic sepsis (q21d) and prerenal azotemia (q14d).

5.8.1.15 Epothilones

Despite the fact that responses to epothilones have been observed in platinum-refractory/resistant ovarian cancer patients, it is not yet clear from phase II/III studies if this class of drugs will play a major role in the treatment arsenal of gynecological cancer patients.

Ixabepilone has received commercial approval in the United States for treatment of refractory breast cancer.

A phase III trial evaluating patupilone in patients with resistant or refractory ovarian, fallopian, or peritoneal cancer compared the efficacy and safety of patupilone (10 mg/m^2 intravenously every 3 weeks) with those of PLD (50 mg/m^2 intravenously every 4 weeks). There was no statistically significant difference in overall survival, the primary endpoint, between the patupilone and PLD arms (HR (95% CI) 0.93, (0.79, 1.09); $p = 0.195$), with median overall survival rates of 13.2 and 12.7 months, respectively. Median PFS was 3.7 months for both arms. The overall response rate (all partial responses) was higher in the patupilone arm than in the PLD arm [15.5% vs. 7.9%, odds ratio (95% CI) 2.11 (1.36, 3.29)] [193].

In a single-institution retrospective review of 60 patients (24 uterine and 36 ovarian cancers), weekly ixabepilone with or without biweekly bevacizumab has promising activity and acceptable toxicity in patients with platinum-/taxane-resistant endometrial and ovarian cancers. This combination warrants further prospective study in these populations [194].

Treatment-related grade 3–4 toxicities include neuropathy, asthenia, neutropenia, and alopecia. The management of these toxicities is not different from that of taxanes.

5.8.1.16 Other Cytotoxic Treatment Modalities

Intraperitoneal Chemotherapy

The intraperitoneal (IP) delivery of cisplatin has been demonstrated in several evidence-based randomized phase III trials to improve overall survival when employed as first-line chemotherapy in patients with small-volume residual advanced ovarian cancer. Despite this fact, the use of IP chemotherapy is still today not accepted by all clinicians as the treatment of choice for optimally debulked EOC. The latter is due to a significantly reduced QoL during treatment with IV/IP versus IV chemotherapy. In the GOG 172 study, patients in the IP/IV group experienced significantly more neurologic side effects and abdominal discomfort. Abdominal discomfort began to improve for both groups during treatment, and no differences in discomfort remained soon after the end of treatment. However, neurologic side effects remained worse in patients in the IP/IV group, even at 1 year after treatment [195].

Substantial local toxicity with abdominal pain and adhesion formation leading to bowel obstruction are of concern, as is the systemic toxicity associated with cisplatin, which remains an issue in case of IV/IP chemotherapy.

The use of IP carboplatin is of particular interest, as it has been documented to have a more favorable toxicity profile compared to cisplatin. Another attractive property of IP carboplatin is that its use makes it easier to deliver in the setting of a busy oncology practice. Unfortunately, there are no comparison data of IP delivery of those two platinum agents showing their equivalence. Currently, phase I studies are ongoing with the IP delivery of carboplatin or paclitaxel [196–198].

Hyperthermic Intraperitoneal Chemotherapy

Locoregional treatments combining cytoreductive surgery and intraperitoneal chemohyperthermia (HIPEC) may improve survival for locoregional disease in the primary treatment of stage III ovarian cancer and in recurrent ovarian cancer.

In the primary setting, no excess toxicity was reported although in the recurrent setting, morbidity and mortality are substantial, with rates between 10% and 50% reported in the literature.

The complications that occur are related to the cytoreductive surgery and the delivered chemotherapy. Postoperative complications can include respiratory failure, bacteremia, renal failure, pyelonephritis, pulmonary embolism, pneumonia, urinary infections, and pyrexia. Complications related to chemotherapy include toxicity of that particular drug (mainly cisplatin, oxaliplatin, mitomycin C). Iterative cytoreductive surgery with HIPEC can be performed; however, strict patient selection is essential, taking into consideration the origin of carcinomatosis, length of recurrence-free interval, age, comorbidity, and likelihood of achieving complete cytoreduction [199–201].

5.8.2 Hormonal Therapy

Many gynecologic cancers, including epithelial and stromal ovarian cancers, endometrial carcinomas, and some gynecologic sarcomas, in particular ESS, express ER and/or PR receptors. Hormonal therapy is in many ways more attractive than

chemotherapy in recurrent or metastatic gynecologic cancers, since the objective of treatment is palliation and prolongation of survival rather than cure.

Endocrine therapy is not associated with the more severe, acute toxicities of chemotherapy and can be administered for prolonged periods with relatively little cumulative toxicity.

There are numerous case reports, retrospective studies, and small phase II studies using a variety of hormonal therapies in this patient population. The most commonly used agents include progestogens, tamoxifen, and luteinizing hormone-releasing hormone (LHRH) agonists. More recently, aromatase inhibitors have also been prescribed [202–205].

Although progestogens have been the mainstay of hormonal treatment in women with recurrent/metastatic endometrial cancer for many years, these agents can be associated with significant adverse effects, including weight gain, hypertension, fluid retention, increased blood sugar, insomnia, tremor, thrombosis, and pulmonary emboli. These can potentially worsen the QoL and may be life-threatening [202].

Many side effects of endocrine therapy, such as hot flushes and mood disturbances, are related to estrogen deprivation and are common to tamoxifen and aromatase inhibitors (AI) (nonsteroidal, anastrozole, and letrozole; steroidal, exemestane). Tamoxifen has estrogenic effects that are beneficial in some tissues; tamoxifen lowers serum cholesterol levels and protects against bone loss and cardiovascular disease but is also associated with potentially life-threatening side effects, such as thromboembolic disease (stroke or pulmonary embolism) and endometrial cancer [204]. Since AIs lack estrogenic activity, they are not associated with these serious adverse events. AIs are also associated with a lower incidence of gynecologic symptoms (vaginal dryness, vaginal bleeding) and hot flushes than tamoxifen. However, AIs are associated with musculoskeletal side effects, such as arthralgia, myalgia, and bone loss, but these events are preventable or manageable [206–209]. In case of hot flushes nonpharmacological approaches such as avoidance of foods or situations that trigger hot flushes, wearing natural fabrics, and employing methods of rapid cooling, such as spray mists or moist wipes, can be effective. The potential benefits of vitamin E and therapies that contain isoflavones have failed to demonstrate any benefit. Data from placebo-controlled clinical trials indicate that the selective serotonin reuptake inhibitors or SSRIs (paroxetine, venlafaxine) are the most effective agents available for the prevention of hot flushes [207].

Vaginal dryness occurs as a result of estrogen deprivation; it can cause pain during intercourse and, subsequently, contributes to loss of libido. Local lubricants can be used temporarily to alleviate symptoms. Topical vaginal estrogen preparations have been shown to relieve the symptoms of vaginal dryness [207].

In postmenopausal women with early breast cancer, postoperative adjuvant AI therapy, which reduces circulating estrogen levels, has been associated with an increased incidence of arthralgia and myalgia compared with tamoxifen or placebo. Although muscular and joint pains are common side effects of AIs, affecting up to 35% of patients, and can be troublesome in some individuals, symptoms are rarely severe enough to necessitate treatment discontinuation, and they usually improve with time. Where necessary, management options are available to help patients to cope with joint and/or muscle pains. Physical strategies, such as physiotherapy or massage, can help to relieve symptoms. Pharmaceutical intervention is limited to

analgesics; nonsteroidal anti-inflammatory drugs, acetaminophen, or cyclooxygenase-2 inhibitors are effective in most patients, although stronger analgesics can be prescribed if necessary [207].

Loss of bone mass is a well-recognized consequence of estrogen deprivation. The recommended treatment depends on the extent of bone loss and includes reassurance, advice on lifestyle changes to slow or prevent further bone loss, such as increasing weight-bearing physical activity and taking dietary supplements (calcium and vitamin D), and drug therapy (e.g., with bisphosphonates in case of severe bone loss).

Hypercholesterolemia and cardiovascular disease have been reported more frequently in patients taking an AI, but there is evidence to suggest that at least some of these effects reflect the absence of tamoxifen's beneficial estrogenic actions on these target tissues rather than a detrimental effect of the AIs. Patients taking an aromatase inhibitor should undergo regular screening for cardiovascular risk factors such as blood pressure monitoring and serum cholesterol measurements as part of routine health checks, but no specific management strategies are required [209].

5.8.3 Targeted Agents

5.8.3.1 EGFR-Targeting Agents

The side effects reported in patients with gynecologic cancers and treated with agents targeting the EGFR are similar to those described in other patient groups.

Acneiform rash is one of the major skin toxicities with agents targeting the EGFR. Preventive measures are protecting the skin with sunscreens, avoiding dry skin, enhancing skin hydration with tocopherol oil or gel, and avoiding tight shoes.

Treatment depends on the grade of toxicity; for grade 1 no specific measures are necessary, while for grade 2 topical antibiotic treatment with clindamycin 1% gel, erythromycin 3% gel/cream, or metronidazole 0.75–1% cream/gel can be used. For pustules, oral semisynthetic tetracycline (minocycline 100 mg/day, doxycycline 100 mg/day) can be used for 4 weeks and until the rash is asymptomatic. For patients with grade 3, topical treatment together with systemic therapy with oral tetracycline and oral corticosteroids (methylprednisolone, 0.4 mg/kg; prednisone, 0.5 mg/kg) for up to 10 days can be combined. For highly symptomatic/nonresponsive patients, treatment with oral retinoids (isotretinoin 0.3–0.5 mg/kg), intravenous corticosteroids (methylprednisolone, dexamethasone), oral/intramuscular/intravenous antihistamines (e.g., chlorphenamine, cetirizine), intravenous antibiotics (amoxicillin/clavulanic acid, gentamicin), or hydration can be considered. In patients with grade 4 skin toxicity, topical treatment can be combined with systemic management with oral retinoids (isotretinoin, 0.3–0.5 mg/kg), intravenous corticosteroids (methylprednisolone, dexamethasone), oral/intramuscular/intravenous antihistamines (e.g., chlorphenamine, cetirizine), intravenous antibiotics (amoxicillin/clavulanic acid, gentamicin), and intravenous hydration [210, 211].

Diarrhea should be treated symptomatically with hydration and anticholinergic drugs (e.g., loperamide). However, anticholinergic drugs should be used with

caution in patients with peritoneal metastasis because it can cause and aggravate gastrointestinal obstruction.

The addition of anti-EGFR monoclonal antibodies to standard anticancer therapy significantly increases the risk of hypomagnesemia [212]; with cisplatin pretreatment especially, this effect can be more pronounced. Asymptomatic hypomagnesemia can be treated with oral replacement therapy. Patients with clinical manifestations of hypomagnesemia should be treated with 50 mEq of intravenous magnesium given slowly over 8–24 h and repeated to maintain the plasma magnesium concentration above 1.0 mg/dL (0.4 mmol/L or 0.8 mEq/L).

The combination with chemotherapy and the pretreatment in most patients with platinum compounds may lead to a higher hematologic toxicity than in non-platinum pretreated patients.

5.8.3.2 Angiogenesis-Interfering Agents

Monoclonal Antibodies

Hypertension (all grades) is one of the most common side effects of bevacizumab or aflibercept. It can be adequately controlled with oral antihypertensive drugs such as angiotensin-converting enzyme inhibitors, diuretics, and calcium channel blockers. The risk of bevacizumab- or aflibercept-associated hypertension does not correlate with the patients' baseline characteristics, underlying disease, or concomitant therapy. For patients with uncomplicated hypertension, the target blood pressure level is <140/90 mmHg. In cancer patients with comorbidities such as chronic kidney disease, a target blood pressure level of <135/85 mmHg should be recommended. Lifestyle modifications such as limiting intake of both saturated and unsaturated fats and salt (maximum 4 g/day) and increasing that of fruits, legumes, and vegetables without changing total caloric input should be encouraged. No clear recommendation for an antihypertensive agent can be made due to lack of studies addressing the subject. Antihypertensive medications that have been effectively used are angiotensin-converting enzyme inhibitors, diuretics, and calcium channel blockers or combinations of them [213].

Proteinuria is also frequently observed in the treatment with bevacizumab against VEGF in other tumor types and was observed in 5% of patients with ovarian cancer [214]. It is due to interference of bevacizumab with VEGF-dependent glomerular endothelial integrity and thrombotic microangiopathy. Monitoring by the use of dipstick urinalyses should be considered in patients treated with bevacizumab, and in case of a positive result, a 24-h urine total-protein collection should be performed. Bevacizumab should be interrupted if urine protein secretion exceeds 2 g/24 h. After recovery, bevacizumab treatment may be restarted. There is no standard pharmacological treatment, but anti-angiotensin agents could be considered as first-line agents in the absence of renal failure, hyperkalemia, or renal artery stenosis [211].

Venous and arterial thromboembolic events were seen in the phase III trial in 7% and 4%, respectively, and were higher than in the control group [16]. Arterial thromboembolic events are a rare but serious complication and include myocardial or cerebrovascular events and peripheral vascular and mesenteric clots. Thrombotic

prophylaxis, including low-molecular-weight heparin (LMWH), warfarin, or aspirin, may be considered in patients starting bevacizumab treatment. Both aspirin and LMWH have been used without increased bleeding complications, while warfarin translates in a higher bleeding complication rate compared to LMWH [214]. Patients with ≥grade 2 arterial thromboembolic events should discontinue bevacizumab while in venous thromboembolic events. Treatment can be temporarily held for grade 3 or asymptomatic grade 4 toxicities. Treatment consists of full anticoagulation, and bevacizumab treatment should be discontinued until stopping anticoagulation.

Hemorrhage occurred in 40% of patients treated with the chemotherapy-bevacizumab combination compared to 12% in the chemotherapy-alone arm and has an important impact on complications depending on the location (2% central nervous hemorrhages) [16]. Bleeding is managed by standard supportive care, while bevacizumab treatment is discontinued [211].

Gastrointestinal perforation has been described in 1–4% of patients with other tumor types. In the phase III study, gastrointestinal perforations were reported somewhat more often in the bevacizumab arm. Also, the rate of intra-abdominal abscess and fistula was higher, but when bevacizumab was given at the start of treatment, it did not lead to a higher complication rate [16]. In patients with recurrent ovarian cancer, risk factors for perforation were previous gastrointestinal surgery, carcinomatosis compromising overall bowel function, intermittent or chronic bowel obstruction, and poor nutrition. Nonsteroidal anti-inflammatory drugs should be avoided when considering bevacizumab treatment. Management of bowel complications after bevacizumab therapy is difficult, and an operative intervention versus conservative management should be carefully considered. The initial management may consist of intravenous antibiotics, bowel rest with nasogastric tube placement, and percutaneous intraperitoneal catheter placement. Increased risk of wound-healing complications is an important consideration when opting for an operative intervention. Bevacizumab treatment is stopped [212]. Similar precautions should be taken with aflibercept.

5.8.3.3 VEGFR Tyrosine Kinase Inhibitors

While perforations are rarely seen with sunitinib, diarrhea has been reported as a frequent side effect (50%), and 2–6% of patients have grade 3/4 diarrhea. Oral hydration and antidiarrheal agents (e.g., loperamide) are the treatments for grade 1 or 2 diarrhea. In patients with grade 3/4 diarrhea, intravenous hydration and electrolyte correction are indicated, and treatment with sunitinib should be interrupted until the diarrhea resolves to ≤grade 1 [211].

Hand-foot syndrome is a frequent reason for dose reduction in the treatment of sunitinib and appears during the first 6 weeks of treatment. Immediate intervention is advised because early symptoms often resolve quickly with minimum effort, allowing continuation of therapy without dose reduction. Pharmacologic interventions such as systemic corticosteroids, vitamin E, pyridoxine, and topical steroids or 99% dimethyl sulfoxide have been reported to be successful. Rapid symptom improvement is observed with temporary cessation of therapy, allowing reinstitution of the drug within 3–14 days [211].

- The incidence of hypothyroidism necessitating thyroid substitution is 12.1 per 100 person-years, and around 13.7% of patients treated with sunitinib will receive thyroid substitution therapy [211]. Therefore, TSH should be checked regularly and is indicated in case of clinical suspicion of hypothyroidism [215].

5.8.3.4 PARP Inhibitors

Olaparib

Oral olaparib (2 × 400 mg/day) has acceptable tolerability when used as maintenance treatment in women with relapsed EOC, and generally side effects are not a reason to discontinue treatment [216]. Toxicities seem consistent across subgroups of BRCA carriers/wild type.

Side effects reported in >10% of patients are gastrointestinal side effects (e.g., nausea, vomiting, diarrhea, dyspepsia, dysgeusia, anorexia), general side effects (e.g., fatigue, headache, dizziness), hematological side effects (e.g., anemia, neutropenia, lymphopenia), and an increase of creatinine [216].

Although gastrointestinal are frequently reported, they are of low grade and do not require prophylactic antiemetic treatment. They can be treated symptomatically with antiemetics and/or by dose interruption or reduction.

Anemia is a frequent side effect that can be of higher grade. A control of hemoglobin at baseline and then monthly during the first 12 months of treatment is recommended.

Long-term monitoring of patients is warranted to determine the potential risk for hematological complications such as myelodysplastic syndrome or acute myeloid leukemia, since olaparib is only used for limited time at this moment [216].

Niraparib

Niraparib (1 × 300 mg/day orally) is indicated as monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy.

Side effect observed in ≥10% of patients receiving niraparib are nausea, thrombocytopenia, fatigue/asthenia, anemia, constipation, vomiting, abdominal pain, neutropenia, insomnia, headache, decreased appetite, nasopharyngitis, diarrhea, dyspnea, hypertension, dyspepsia, back pain, dizziness, cough, urinary tract infection, arthralgia, palpitations, and dysgeusia.

The most common serious adverse reactions >1% (treatment-emergent frequencies) are thrombocytopenia and anemia.

It is therefore recommended to monitor complete blood counts weekly during the first month of treatment and modify the dose as needed. After the first month, it is recommended to monitor blood counts monthly and periodically after this time. Based on individual laboratory values, weekly monitoring for the second month may be warranted.

If side effects occur a first time, it is advised to interrupt the treatment (but no longer than 28 consecutive days) to allow the patient to recover from the adverse reaction and then restart at the same dose. In the case that the adverse reaction

recurs, it is recommended to reduce the dose. If adverse reactions persist beyond a 28-day dose interruption, it is recommended to discontinue niraparib [217].

5.8.3.5 Check Point Inhibitors

Pembrolizumab

Although pembrolizumab has not been registered for the treatment of gynecological cancer, its activity has been reported in MSI-H/dMMR tumors of the uterus and cervix [41] and in patients with a GNT failing several lines of chemotherapy [78].

It is administered as an intravenous infusion over 30 min every 3 weeks in a dose of 2 mg/kg until progression or unacceptable toxicity.

It induces immune-related side effects including immune-related pneumonitis, colitis, hepatitis, nephritis, endocrinopathies, including hypophysitis, type 1 diabetes mellitus, diabetic ketoacidosis, hypothyroidism, and hyperthyroidism, and skin reactions.

Most immune-related adverse reactions occurring during treatment with pembrolizumab are reversible and managed with interruptions of pembrolizumab, administration of corticosteroids and/or supportive care [218].

Conclusion

Gynecologic cancers are an important cancer in women. They consist of different entities that are treated with different treatment modalities, including drug treatment. Since the long-term survival of these patients, it is important to deal not only with acute but also with long-term side effects. They should be prevented if possible or treated adequately to ensure a maximal QoL.

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Side Effects of Medical Cancer Therapy in Genitourinary Malignancies

6

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Abstract

Genitourinary cancers represent 12.8% of cancer in both sexes and 21.5% in men, accounting for 7% of cancer deaths in both sexes and 10.5% in men. The systemic treatment of prostate cancer and renal cell carcinoma does not rely on chemotherapy, with the exception of taxane docetaxel and cabazitaxel. Prostate cancer is primarily treated by androgen deprivation, by surgical castration or LHRH analogs, or by androgen receptor pathway inhibitor enzalutamide and abiraterone acetate. Renal cell carcinoma is nowadays treated with agents targeting survival and angiogenesis pathways, including tyrosine kinase inhibitors (TKIs) sorafenib, sunitinib, axitinib, and pazopanib; anti-vascular endothelial growth factor (VEGF) monoclonal antibody bevacizumab; mammalian target of rapamycin (mTOR) inhibitors temsirolimus and everolimus; and oral inhibitor of tyrosine kinases MET, VEGFR, AXL, cabozantinib. Most recently, immune checkpoint inhibitors have made their way to genitourinary cancers, revolutionizing the treatment of urothelial cancers and renal cell carcinoma.

Hormone therapies and targeted therapies don't eradicate prostate cancer and renal cell carcinoma but rather switch them to a more chronic state. This means that these treatments are prescribed chronically for an extended period of time. In such conditions, even the least bothersome side effect may profoundly alter the quality of life of patients. Ultimately, this is a threat to compliance and then to the efficacy of these treatments. In addition, many of the side effects of these drugs often overlap with common chronic illnesses such as diabetes, hypertension, hypercholesterolemia, heart failure, and osteoporosis. An exhaustive knowledge of these side effects, proper monitoring, and in-depth education of patients are key elements to secure the efficacy of these treatments.

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M. A. Dicato, E. Van Cutsem (eds.), *Side Effects of Medical Cancer Therapy*,
https://doi.org/10.1007/978-3-319-70253-7_6

Keywords
Prostate cancer · Renal cell carcinoma · Androgen deprivation therapy · Tyrosine kinase inhibitors · mTOR inhibitors · Side effects

6.1 Introduction

Genitourinary cancers are the leading forms of cancer and cancer deaths. Based on GLOBOCAN, 345,195 prostate cancers, 97,193 bladder cancers, 54,281 kidney cancers, and 18,202 testis cancers have been reported in the European Union in 2012, accounting for 36% of cancers [1]. Owing mainly to major improvements in treatment modalities, which include surgery, radiotherapy, and innovative systemic treatments, genitourinary cancers account for only 17% of cancer deaths.

Two genitourinary malignancies, prostate cancer (PCa) and renal cell carcinoma (RCC), are characterized by a limited usage of chemotherapy, in contrast to other cancer types. PCa is primarily treated by hormone therapy, mainly androgen deprivation therapy (ADT). In localized disease, ADT is used primarily in adjuvant to radiotherapy and surgery, a setting in which in dramatically increases overall survival (OS) [2]. In metastatic disease, ADT rarely controls the disease beyond a few months. Then the disease becomes castration-resistant, a stage still today uniformly lethal. The prognosis of metastatic castration-resistant prostate cancer (mCRPC) has been substantially improved by the development of several drugs: two taxane chemotherapies, docetaxel and cabazitaxel; two androgen receptor (AR) pathways inhibitors, abiraterone acetate and enzalutamide, a bone-seeking α-emitter radionuclide, Ra223; and two bone-protecting agents, zoledronic acid and denosumab [3]. In 2004, the median OS of mCRPC patients in the mitoxantrone arm of TAX-327, the docetaxel registration trial, was 16.5 months [4]. In 2017, the median OS of mCRPC treated with enzalutamide as a first line of treatment is 35.6 months [5]. The most interesting development, however, is the recent publication of four trials demonstrating an unprecedented benefit when ADT is combined with either docetaxel or abiraterone at diagnosis in newly diagnosed metastatic PCa [6–9]. CHAARTED and STAMPEDE have investigated the benefit of adding six cycles of docetaxel, at the standard dose of 75 mg/m^2 to ADT [8, 9]. The hazard ratio (HR) for OS when adding docetaxel to ADT was 0.61 and 0.78. The LATITUDE trial has tested a combination of ADT with abiraterone and prednisone 5 mg in 1199 newly diagnosed men with high-risk metastatic PCa (≥2 of Gleason score ≥ 8, visceral disease, ≥3 bone metastases) [6]. The combined treatment was shown to extend median OS from 34.7 months in the ADT group to "not reached" (HR 0.62; $P < 0.001$). The STAMPEDE trial tested the same combination in a broader group of 1917 patients; 20% were node-positive, 27% had high-risk locally advanced disease, and 5% demonstrated PSA recurrence [7]. The combined treatment significantly decreased the number of deaths from 262 with ADT alone to 184 (HR 0.63; $P < 0.001$). The 3-year survival was 83% in the combined treatment group and 76% in the ADT arm, with a HR of 0.61 for metastatic PCa.

Renal cell carcinoma (RCC), and especially its most frequent subtype, clear cell carcinoma, is an even more peculiar disease, being both radio- and chemoresistant. RCC used to be considered an immune-sensitive tumor, since the only active treatments, although of limited value, were interferon-α (Ifα) and high-dose interleukin (HD-IL2). A better understanding of the importance of the VHL/HIF hypoxia pathways has fueled the development of drug-targeting angiogenesis and survival pathways that have revolutionized the treatment of advanced RCC. Today, seven drugs have supplanted Ifα and HD-IL2: sorafenib, sunitinib, temsirolimus, everolimus, bevacizumab, pazopanib, and axitinib. This is without counting the introduction of immune checkpoint inhibitors, nivolumab and others, whose toxicity and monitoring will be described elsewhere. Although many of these drugs confer little or no OS benefit, they have been widely accepted, and it is estimated that overall the life span of patients has been extended. But new modes of actions have brought new types of side effects, to which physicians and patients need to become accustomed. These will be reviewed in the second part of this chapter.

Because several other chapters will address the toxicity of chemotherapy and immune check point inhibitors, we have chosen not to cover that topic and focus on hormone therapy of PCa and targeted therapies of RCC.

6.2 Side Effects of Hormonal Treatments in Prostate Cancer

6.2.1 Androgen Deprivation Therapy

Androgen deprivation therapy (ADT) by means of surgical castration or estrogens has been the standard treatment of advanced symptomatic prostate cancer since the seminal work of Charles Huggins in the late 1940s [10]. ADT is primarily used alone in advanced PCa or concomitantly and adjuvant to external beam radiation therapy (EBRT), for duration ranging from 6 months to 3 years [11].

Resulting from significant improvements in the treatment advanced PCa, ADT is nowadays prescribed for longer duration, and thus the patients are much exposed to its side effects. ADT is traditionally recognized through its acute side effects, which include loss of libido and erectile dysfunction, hot flushes, fatigue, and psychological effects such as emotional instability, depression, or cognitive dysfunction [12–14]. Recently, however, more attention has been given to long-term toxicity, including anemia, accelerated bone loss leading eventually to osteoporosis and fragility fractures, and sarcopenic obesity, which may lead to an increased risk of cardiovascular morbidity and mortality [14].

6.2.1.1 Short-Term Adverse Events of ADT

Hot Flushes

Hot flushes are described as sudden and uncomfortable heat sensations in the face, neck, upper chest, and back, lasting from seconds up to an hour. Hot flushes are the most common side effect, affecting by up to 80% of patients, but also among the

most bothersome and disrupting for the everyday life [13]. Hot flushes are often triggered by stress, heat, sudden changes in body position, ingestion of warm or spicy food, or smoking [13].

Management of hot flushes includes informing patients or situations or behaviors that can induce or aggravate them. Standard scale, such as the Moyad questionnaire, can be used to record frequency and severity of hit flushes [15]. If hot flushes are very bothersome for patients, medical therapy can be considered. Hormonal agents such as megestrol acetate, medroxyprogesterone acetate, cyproterone acetate, and low-dose diethylstilbestrol are very popular to treat bothersome hot flushes [12, 13, 16, 17]. Selective serotonin reuptake inhibitors (SSRIs) (i.e., venlafaxine or citalopram), (alpha) α-adrenergic inhibitors (i.e., clonidine), and GABA analogue gabapentin are alternatives to hormonal agents, although their efficacy is usually lower [18–20]. Acupuncture and phytotherapy, especially sage extracts, can eventually be recommended to patients, despite lack of definitive robust scientific evidence [21, 22].

Sexual Dysfunction

The extent of sexual dysfunction varies widely from one patient to another. The negative impact of ADT on libido and sexual function is well known, including decrease of sexual desire and impotence [23]. Patients and their partners should be informed about this, as it can cause anxiety for both, although a satisfying sexual and affective life is still possible under ADT. From a historic review of the social and intellectual performances of eunuchs, Aucoin and Wassersug suggested that, with the right cultural setting and individual motivation, ADT may actually enhance, rather than hinder, both social and sexual performance [24]. But it is important to inform and educate the patients. Walker et al. have piloted a randomized controlled trial in 27 couples to investigate the effect of an educational intervention designed to preserve couples intimacy in the face of ADT [25]. While results were not statistically significant, trends and effect sizes suggest that the educational intervention helped attenuate declines in intimacy for patients, but not for their partners. Couples who participated in the intervention were more successful at maintaining sexual activity than were couples in the control group. Traditional treatments of erectile dysfunction can be recommended in ADT-treated patients, including intracavernous injections of prostaglandins and/or phosphodiesterase-5 inhibitors. Physicians should always remember that ADT induces first a libido problem and that patient and partner counseling may prove as effective as medications.

Fatigue

Fatigue is one of the most common side effects of ADT. Although fatigue is very difficult to fight, lifestyle changes and especially physical exercise may help to alleviate fatigue and improve quality of life. A systematic review and meta-analysis of 16 randomized controlled trials involving 1574 PCa patients confirms that exercise has a beneficial effect on cancer-related fatigue [26]. The FRESH START trial has randomized 543 subjects with newly diagnosed locoregional breast or prostate cancer to receive a 10-month specific program promoting diet changes and physical

exercise or nonspecific information. Although subjects in both arms significantly improved their lifestyle behavior, significantly greater improvement was observed in subjects receiving the diet- and exercise-specific information [27]. Physicians should convince patients to adopt a healthier lifestyle including a healthy diet and physical exercise. Fatigue may be further aggravated by sarcopenia (loss of skeletal muscle mass) resulting from ADT, which directly impacts on muscle strength and reduces physical activity [28].

Cognitive and Psychological Side Effects

ADT may cause psychological side effects such as reduced cognitive function (e.g., reduced concentration and memory problems), emotional instability, and even depression [13, 16]. Patients and relatives should be informed about the likelihood of emotional changes and how to identify early signs of depression or decreased cognitive function in order to ensure rapid referral to a specialist. It is also important to explain these side effects to the patient's family so that they understand their nature and origin and can help the patient adapt to them. In some patients, these emotional disturbances may evolve into depression. Depression can be severe and can lead to an increased risk of suicide in the months following diagnosis of advanced PCA, probably as a mixed effect of the cancer diagnosis and the initiation of ADT [29]. Dinh et al. have conducted a survey on 78,552 men older than 65 years with localized PCa, including 43% that received ADT, using the SEER-Medicare Linked Database [30]. ADT patients, in comparison with non-ADT patients, had a higher 3-year cumulative incidences of depression (7.1% vs. 5.2%, respectively), inpatient psychiatric treatment (2.8% vs. 1.9%, respectively), and outpatient psychiatric treatment (3.4% vs. 2.5%, respectively). Adjusted Cox analyses demonstrated that patients on ADT had a 23% increased risk of depression and a 29% increased risk of inpatient psychiatric treatment. The risk of depression increases with duration of ADT, from 12% within 6 months of treatment, 26% within 7–11 months, and to 37% within 12 months of treatment. Based on this information, it is recommended to screen for patients with preexisting depression before starting them on ADT using validated scale such as the PHQ-9 questionnaire [31].

The impact on cognitive functions, dementia, and, more specifically, the specific risk of Alzheimer's disease has also grown as a concern. Wu et al. have conducted an in-depth survey on 39 PCa patients, including 10 on ADT [32]. Overall, ADT-receiving patients experienced marginally more cognitive problems than those not receiving ADT (non-ADT) even though there were no significant differences between groups in neuropsychological performance. ADT patients also experienced more declines in prospective memory and multitasking than non-ADT patients. Significant proportions of participants in both groups also experienced retrospective memory, attention and concentration, and information processing difficulties. With respect to neurobehavioral symptoms, more ADT patients experienced emotional lability and impulsivity (both aspects of disinhibition) than non-ADT patients. Nead et al. have conducted a systematic review of the literature reporting the outcome of dementia in ADT-treated PCa [33]. That analysis, which included nine studies, showed an increased risk of dementia among ADT users (HR 1.47), both all-cause

dementia (HR 1.46) and Alzheimer's disease (HR 1.25). The potential for neurocognitive deficits secondary to ADT should be discussed with patients and evaluated prospectively. The association with Alzheimer's disease has been confirmed by Jhan et al. on data from 24,360 Taiwanese PCa patients [34]. During the average 4-year follow-up period, the incidence of Alzheimer was 2.78 per 1000 person-years in the non-ADT cohort and 5.66 per 1000 person-years in the ADT cohort. After adjusting for age and all comorbidities, the combined ADT cohort was found to be 1.84 times more likely to develop Alzheimer than the non-ADT control group ($p < 0.001$).

6.2.1.2 Long-Term Adverse Events of ADT

Anemia

Hemoglobin level will drop by 10% in at least 90% of ADT patients [35]. Anemia is usually normocytic, normochromic, and due to the lack of androgen stimulation of erythroid precursors and a decrease in erythropoietin production. Anemia worsens fatigue [13]. Physicians should closely monitor hemoglobin levels in patients treated with ADT. Anemia may be aggravated by extensive invasion of the bone marrow, which frequently occurs in mCRPC patients.

Metabolic and Cardiovascular Side Effects

The relationship between ADT and an increased risk of cardiovascular disease (CVD) is intensively disputed since large epidemiological survey and prospective trials provide controversial results. In addition, two different aggravating factors coexist: an acute effect of testosterone, FSH, or GnRH flare on atherosclerotic disease and long-term consequences of metabolic changes. The first maybe a class effect of GnRH agonists, not seen with GNRH antagonists; the second probably linked to any mechanisms of testosterone suppression.

Acute Cardiotoxicity of ADT

In patients with a previous history of cardiovascular events (CVE), even short-term course of ADT may significantly increase the risk of presenting a new CVE. In 2009 already, Nanda et al. analyzed 5077 localized PCa and found that neoadjuvant ADT was associated with an increased risk of all-cause mortality among men with a history of coronary artery disease (CAD), induced congestive heart failure (CHF), or myocardial infarction (MI) but not among men with no comorbidity or a single risk factor [36]. In the subgroup of patients with CAD, CHF, or MI, 26.3% deaths were reported in ADT-treated patients and 11.2% deaths in non-ADT-treated controls (HR 1.96; $P = 0.04$). Interestingly, the difference comes from death occurring with 2 years of initiation of treatment, suggesting an early mechanism.

This acute toxicity is pharmacology dependent, since it is less frequent with GnRH antagonists, which don't produce an initial flare of testosterone, FSL, and LH. Albertsen et al. have analyzed pooled data from 2328 patients collected in 6 phase 3 prospective randomized trials comparing the efficacy of GnRH agonists ($n = 837$) against GnRH antagonists ($n = 1491$) [37]. Noteworthy, among men with

preexisting CVD, the risk of a new CVE within 1 year of initiating therapy was significantly lower among men treated with a GnRH antagonist compared with GnRH agonists (HR 0.44; $p = 0.002$). The mechanism underlying this class effect is probably complex and involves the potential roles of testosterone flare, GnRH receptors outside the pituitary gland, and altered levels of follicle-stimulating hormone [38]. Recently, Scailteux et al. have analyzed data from 35,118 new French ADT users and found no meaningful difference in cardiovascular risk between GnRH antagonist and agonists [39]. It is fair pointing, however, that the paper included a very small number of patients treated with GnRH antagonists.

ADT-Induced Metabolic Disturbances and Cardiovascular Disease

ADT causes changes in the patient's body mass and composition [13, 28]. Suppression of testosterone causes a situation known as sarcopenic obesity, combining muscular atrophy and an increase in fatty tissue [40, 41]. By creating an imbalance between lean and fatty mass, sarcopenic obesity induces many of the phenotypic features of the metabolic syndrome, such as increased subcutaneous fat, increased total and high-density lipoprotein (HDL) cholesterol, and increased adiponectin levels [42, 43]. The main cause of these metabolic changes is an increased peripheral resistance to insulin, leading to type 2 diabetes [44]. These metabolic changes may be facilitated by reduced physical activity resulting from fatigue and depression.

Impact of Metabolic Changes on Cardiovascular Events

In an observational study on 37,443 men, Keating et al. reported that ADT significantly increases the risk of diabetes (HR 1.28), coronary heart disease (CHD) (HR 1.19), myocardial infarction (MI) (HR 1.28), sudden death (HR 1.35), and stroke (HR 1.22) [45]. Combined androgen blockade and orchiectomy further increased these risks; in contrast, pure oral antiandrogen monotherapy had no detectable impact. Since that first large analyses, there has been a controversy fueled by observation made in prospective trials and in large retrospective survey (Fig. 6.1). Bosco et al. have performed a meta-analysis using observational data from eight observational studies including at least one type of ADT and a nonfatal or fatal CVD outcome [46]. The relative risk (RR) of any type of nonfatal CVD was 1.38 for men with PCa on GnRH agonists, compared with men not treated with ADT. When analyzing nonfatal ischemic heart disease only, the RR was 1.39. The RR between GnRH agonists and nonfatal or fatal myocardial infarction (1.57) or stroke (1.51) were even stronger. In contrast, systematic review and meta-analysis of randomized trials have failed to demonstrate a link between ADT and cardiovascular disease. In the meta-analysis by Nguyen et al., among 4141 patients from 8 randomized trials, CV death was not significantly different in patients receiving ADT vs. control (RR, 0.93; $P = 0.41$) [47]. ADT was not associated with excess CV death in trials of at least 3 years (long duration) of ADT (RR 0.91; P 0.34) or in trials of 6 months or less (short duration) of ADT (RR 1.00; P 0.99). Although RCTs usually provide the highest grade of evidence for the assessment of the effectiveness of therapy, these

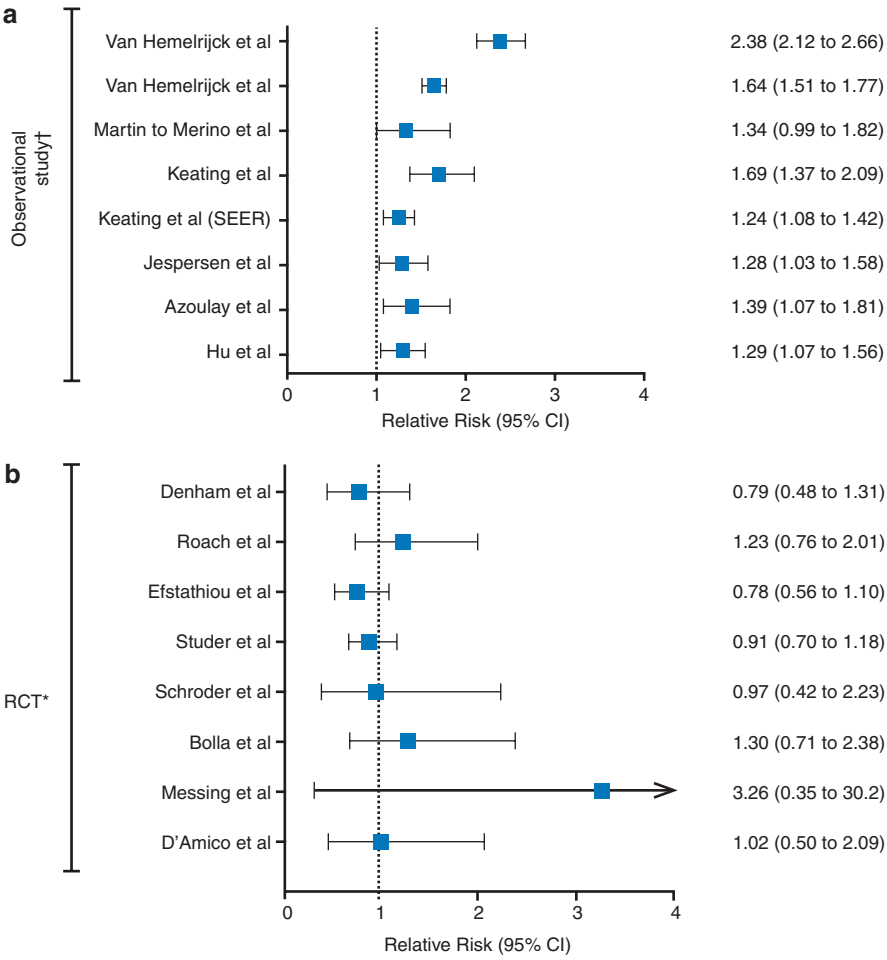

Fig. 6.1 Forest plot for the association between GnRH agonists and nonfatal or fatal myocardial infarction in epidemiological retrospective surveys (**a**, adapted from [46]) and in prospective randomized controlled trials (**b**, adapted from [47]). *RCT* randomized control trial; *SEER* surveillance, epidemiology, and end results; *CI* confidence interval; *MI* myocardial infarction; *RR* relative risk; *SEER* surveillance, epidemiology, and end results

trials tend to exclude older patients or those with a higher number of comorbidities. For instance, in the aforementioned analysis by Nguyen et al., authors highlight that given that they analyzed phase 3 RCTs, it is likely that participants had fewer comorbidities than the general population, making them less susceptible to ADT-related CV adverse effects [47].

Whether there is a causal relationship between ADT and cardiovascular morbidity and mortality remains controversial and continues to be studied. However, at this

point in time, experts believe that it is reasonable to state that there may be an association between ADT and cardiovascular events and death because of the adverse effect of ADT on risk factors for cardiovascular disease [48]. On October 20, 2010, the US Food and Drug Administration (FDA) notified the manufacturers of the GnRH agonists of the need to add new safety information to the warnings and precautions section of the drug labels [49]. This new information warns about increased risk of diabetes and certain cardiovascular diseases (heart attack, sudden cardiac death, stroke) in men receiving these medications for the treatment of prostate cancer.

Monitoring and Prevention of Cardiovascular Events

Physicians should carefully monitor the metabolic and cardiovascular parameters of patients treated with ADT, including blood pressure, serum lipid level, and hemoglobin and fasting serum glucose levels [12, 13, 15, 16, 50]. Physicians should encourage patients to adopt a healthier lifestyle, including an appropriate low-fat diet and regular physical exercise. Nobes et al. have investigated the effects of metformin and lifestyle changes on the development of ADT-related metabolic changes [51]. In total, 40 men scheduled to receive 6 months ADT have been randomized between standard care and 6 months of metformin, a low glycemic index diet, and an exercise program. After 6 months, significant improvements in abdominal perimeter, weight, body mass index, and systolic blood pressure were seen in the intervention arm compared to controls.

Resistance training is a form of strength training in which each effort is performed against a specific opposing force generated by resistance. Resistance exercise is used to develop the strength and size of skeletal muscles. Properly performed, resistance training can provide significant functional benefits and improvement in overall health and well-being. Studies conducted by Galvão et al. demonstrated that 20 weeks of progressive resistance exercise performed in a rehabilitation clinic increased muscle strength and endurance and preserved whole-body lean mass with no change in fat mass [52]. Segal et al. demonstrated that men assigned to resistance exercise had less interference from fatigue on activities of daily living and a better quality of life than untrained men [53]. The same group demonstrated that a combination of both resistance and aerobic exercise mitigates fatigue in patients treated by EBRT with or without ADT [54]. Resistance exercise generated longer-term improvements and additional benefits for quality of life, strength, triglyceride levels, and body fat. Baumann et al. have performed a meta-analysis of 25 randomized controlled trials regarding physical activities in prostate cancer patients, including 21 investigating exercise interventions during the phase of medical treatment and 4 during the aftercare [55]. This meta-analysis suggests that incontinence, fitness, fatigue, body constitution, and also quality of life can be improved by clinical exercise in patients during and after prostate cancer treatment. Only four studies, all conducted during medical treatment, reached the level “1b” and concluded that “supervised” exercise is more effective than “non-supervised” exercise.

Skeletal Complications of ADT

Cancer Treatment-Induced Bone Loss (CTIBL) and ADT

The association between surgical castration and accelerated bone loss, and the fact that administration of estrogens does not prevent this, was first described more than 15 years ago [56]. Longitudinal studies suggest that bone loss accelerates after the age of 70 years in men, probably related to the decrease in testosterone and estradiol levels observed in aging males [57–59]. Prospective studies measuring bone loss associated with ADT have been performed for more than 10 years and have consistently observed a significant deterioration of bone mineral density (BMD) over time (Table 6.1). Substantial bone loss begins very early in the course of treatment with ADT. Mittan et al. reported that, in comparison to 15 age-matched untreated controls, the concentration of urinary N-telopeptide (uNTx, a biomarker for bone resorption) in patients receiving ADT was significantly higher after 6 months of treatment, indicative of an early bone loss [64].

ADT and Fragility Fractures

Several epidemiologic studies have confirmed that CTIBL increases the risk of fragility fractures (Table 6.2), which in turn may decrease survival. Several risk factors for fragility fractures have been identified, the most important being the duration of ADT. In a Cox proportional hazards analysis of Shahinian's epidemiologic survey, there was a statistically significant relation between the duration of ADT and the subsequent risk of fractures [65]. The relative risk of any fracture was 1.07 for patients receiving 1–4 doses of trimonthly GnRH agonists, 1.22 for 5–8 doses, 1.45 for ≥9 doses, and 1.54 for patients treated by orchiectomy. In addition to ADT duration, other risk factors for fractures include race and low body mass index (<25 kg/m^2) [68]. In Alibhai's survey, independent predictors of fragility and any fracture were increasing age, prior bone thinning medications, chronic kidney disease, prior dementia, prior fragility fractures, and prior osteoporosis diagnosis or treatment ($p < 0.05$) [67].

Table 6.1 Prospective studies measuring bone loss associated with ADT

Study	Treatment	BMD decrease at 12 months (%)
Eriksson 1995 [56]	Orchiectomy	Hip: 9.6 Radius: 4.5
Maillefert 1999 [60]	GnRH agonist	Hip: 3.9 Lumbar spine: 4.6
[61]	Orchiectomy GnRH agonist	Hip: 2.4
Daniell 2000 [62]	GnRH agonist	Hip: 0.6 Lumbar spine: 2.3
Higano 2004 [63]	LHRH agonist + antiandrogen	Hip: 2.7 Lumbar spine: 4.7
Mittan 2002 [64]	GnRH agonist	Hip: 3.3 Radius: 5.3

Table 6.2 Reported fracture risk in patients receiving hormone therapy[a]

Study	Patients (*n*)	ADT duration (years)	Fracture risk (%)					
			All sites		Hip		Hospitalization	
			ADT	No ADT	ADT	No ADT	ADT	No ADT
Shahinian et al. [65]	50,613	1–5	19.6	12.6	4.06	2.06	5.19	2.37
Smith et al. [66]	11,661	>12	7.88[b]	6.51[b]	1.26[b]	0.98[b]		
Alibhai et al. [67]	19,079	6,7	17.2	12.7	2.6	2	8	5.7

ADT androgen deprivation therapy
[a]Rate (%) per person per year
[b]$p < 0.05$

Monitoring and Prevention of CTIBL in ADT-Treated Patients

Since bone loss occurs rapidly during ADT, physicians should inform patients and take all appropriate measures to monitor and minimize bone loss as early as possible during treatment. Early diagnosis of bone loss and treatment to improve bone health are important to protect patients from fractures, which are difficult to heal in mature adults.

Dual-energy X-ray absorptiometry (DXA) should be used to monitor the spine, hip, or total body BMD. The spine is the preferred site of densitometry for serial measurement of bone mass to monitor changes in BMD [69]. When spine measurements are technically invalid, especially in the presence of bone metastases, total hip BMD should be assessed [69]. Status of bone health is typically based on the T-score measurement that compares a patient's BMD to that of a 30-year-old healthy person (baseline). For every standard deviation below this baseline, the relative risk of fracture increases from 1.5- to −2.5-fold. A patient with a T-score above −1 is considered to have healthy bone, a score of −1 to −2.5 is osteopenic, a score below −2.5 is osteoporotic, and a score below −2.5 with any associated fracture is considered severely osteoporotic [70]. A patient with a T-score below −2.5 has approximately an 11-fold increase in the risk of developing a fracture than a patient with normal BMD [71]. There is no uniform recommendation about when to perform the first DXA scan in patients treated with ADT. The European Association of Urology (EAU) guidelines recommend performing the first DXA scan before long-term ADT is initiated, but there is no cutoff duration defining long-term ADT and no recommendation on scheduling of subsequent DXA scans [11]. Similarly, physicians should be attentive to the presence of additional risk factors, as highlighted by Ebeling (Table 6.3) [70].

Table 6.3 Risk ratio for hip fracture according to risk factors adjusted for age and for bone mineral density in men and women

Risk factor for hip fracture	Adjusted risk ratio (95% CI)
Low or high BMI	
20 vs. 25	1.42 (1.23–1.65)
30 vs. 25	1.00 (0.82–1.21)
Prior fracture at >50 years of age	1.62 (1.30–2.01)
Parental history of hip fracture	2.28 (1.48–3.51)
Current smoking	1.60 (1.27–2.02)
Use of systemic corticosteroids for >3 months	2.25 (1.60–3.15)
Excessive alcohol use	1.70 (1.20–2.42)
Rheumatoid arthritis	1.73 (0.94–3.20)
Low testosterone	
Hip fracture	1.88 (1.24–2.82)
Other non-vertebral fracture	1.32 (1.03–1.68)

Adapted from reference [70]

Prevention and Treatment of CTIBL in ADT-Treated Patients

Patients should be encouraged to make specific lifestyle changes: cessation of smoking, moderate alcohol and caffeine consumption, and regular weight-bearing exercises [13]. Patients should also be encouraged to consume a healthy diet of foods and beverages containing calcium (dairy) and vitamin D (fatty fish). The recommended daily intake of calcium should be 1200–1500 mg, and serum levels of hydroxyvitamin D should be maintained at ≥30 ng/mL [70, 72]. If required, supplementation with cholecalciferol at doses of 800–2000 IU/day should be given. A systematic review of around 64,000 men and women showed that a daily intake of calcium (≥1200 mg) or calcium with vitamin D (≥800 IU daily) reduced the frequency of osteoporotic fractures by 12% in men and women aged ≥50 years [73]. Physical exercise is also a very important part of preventing bone loss. Resistance exercise is particularly favorable for maintaining or improving bone mass and architecture while also being safe for older people [74].

Osteoporosis is a disease that needs to be treated appropriately. The last posted version of the National Comprehensive Cancer Network (NCCN) guideline on prostate cancer advises pharmacologic treatment for men when the 10-year probability of hip fracture is ≥3% or major osteoporosis-related fracture is ≥20% [75]. The NCCN guidelines recommend assessing fracture risk using the FRAX algorithm (www.shef.ac.uk/FRAX/index.htm) by considering CTIBL as "secondary osteoporosis." The FRAX algorithm, however, has never been prospectively validated on a cohort of ADT-treated men.

Bisphosphonates

Pamidronate (at a dose of 60 mg IV every 12 weeks) was the first bisphosphonates to be studied for the prevention of CTIBL in prostate cancer in a randomized controlled trial [76]. After 1 year, BMD decreased by 3.3% at the lumbar spine ($p < 0.001$) and by 1.8% at the hip ($p > 0.005$) in untreated patients. No change in BMD occurred in patients receiving pamidronate. Fracture rate was not reported.

Two double-blind, randomized, placebo-controlled clinical trials have evaluated the effect of zoledronic acid on BMD in ADT-treated patients with nonmetastatic prostate cancer. In the first trial, patients received zoledronic acid, 4 mg, or placebo IV every 3 months for 1 year [77]. Mean lumbar spine BMD increased by 5.6% in men receiving the bisphosphonate ($n = 42$) but decreased by 2.2% in the placebo group ($n = 37$) ($p < 0.001$). The second trial evaluated the efficacy of a 4-mg annual zoledronic acid infusion [78]. Mean BMD of the lumbar spine increased by 4.0% with the bisphosphonate and decreased by 3.1% with the placebo ($p < 0.001$); the total hip BMD increased by 0.7% with the bisphosphonate and decreased by 1.9% with placebo and ($p = 0.004$). To date, none of the studies with zoledronic acid have demonstrated a benefit on fractures.

The oral bisphosphonate alendronate, at the weekly dosage of 70 mg, has also been tested in 44 men, of whom 39% had osteoporosis and 52% had low BMD at baseline [79]. In men treated with alendronate, BMD increased over 1 year by 3.7% ($p < 0.001$) at the spine and 1.6% ($p = 0.008$) at the femoral neck. Among men in the

placebo group, there were reductions in BMD of 1.4% ($p = 0.045$) at the spine and 0.7% ($p = 0.081$) at the femoral neck.

Low-Dose Denosumab

Denosumab is a fully human monoclonal antibody that specifically inhibits RANKL, a critical mediator of osteoblast-to-osteoclast crosstalk. Injections of denosumab result in a prolonged inhibition of bone remodeling in postmenopausal women [80]. A prospective, randomized, placebo-controlled study has investigated the benefit of denosumab in the prevention of CTIBL and fractures in 1400 patients with nonmetastatic PCa receiving ADT [81]. To be eligible for the study, patients had to be 70 years of age or older or alternatively had either a low BMD (T-score at the lumbar spine, total hip, or femoral neck of less than −1.0) at baseline or history of an osteoporotic fracture. Denosumab was administered every 6 months subcutaneously at a dose of 60 mg. After 24 months BMD at the lumbar spine had increased by 5.6% in the denosumab group as compared with a loss of 1.0% in the placebo group ($p < 0.001$). Patients who received denosumab had a decreased incidence of new vertebral fractures at 36 months (1.5% vs. 3.9% with placebo) (relative risk: 0.38; 95% CI 0.19–0.78; $p = 0.006$). The rates of adverse events were similar between the two groups. Recently, denosumab was approved for the management of bone loss associated with treatment of prostate cancer.

Checklist for Monitoring Patients Receiving ADT

Before initiating treatment:

- Inform the patient about the occurrence of hot flushes, and provide lifestyle recommendations to avoid excessive triggering.
- Inform the patient and his partner about libido, mood, and cognitive changes.
- Encourage maintaining and even increasing social activities and networking, possibly referring to patient support groups.
- Inform in due time the patient's general practitioner, cardiologist, and endocrinologist about initiation of ADT. Advise the patient to schedule a follow-up visit with these specialists within 6 months.
- Provide dietetic counseling and recommend resistance exercise. This will be done optimally by referring the patient to a dietician and physical therapist or by administrating a specifically designed coaching program.
- Search for risk factors of bone loss, and perform an immediate DXA scan, if they are present.

During treatment:

- In addition to PSA and testosterone measurements and imaging studies that are required for oncologic follow-up, it is recommended to measure weight and abdominal perimeter (or preferably body fatty tissue content by impedance technique), blood pressure, and dose hemoglobin, fasting cholesterol (total and

HDL), triglyceride, and glucose levels. In case of abnormalities refer the patient to a specialist.
- Advise a DXA scan after 1–2 years of ADT.

6.2.2 Modern AR Pathway Inhibitors

As mentioned in the introduction, the clinical development of abiraterone acetate and enzalutamide has profoundly reshaped the management of advanced prostate cancer [3]. Both agents are orally available, thus very convenient, and present limited toxicity which made them optimal first-line candidate in mCRPC patents. Several trials are on their way to test earlier use of these drugs. However, they both have specific side effects that the physician needs to know in order to secure long-term safety and compliance.

6.2.2.1 Abiraterone Acetate

Abiraterone acetate is an androgen synthesis inhibitor that increases OS in mCRPC patients [82, 83]. Abiraterone's mode of action is different from LHRH agonists and antagonists since it targets CYP17, a key enzyme that mediates androgen synthesis in the testes and adrenal glands. Abiraterone not only inhibits the synthesis of androgens but also suppresses cortisol synthesis [84]. This induces a reciprocal increase in the pituitary adrenocorticotropic hormone (ACTH) and therefore an elevation of corticosterone. This may lead to fluid retention, hypokalemia, and hypertension. To prevent these side effects, abiraterone must be combined with corticosteroids such as prednisolone, prednisone, or dexamethasone. The standard dose of corticosteroid use in mCRPC is 5 mg bid of prednisolone and prednisone. At that dose, grade 1–4 fluid retention or edema was seen in 28% of the patients (vs. 24 with prednisone 5 mg bid alone), hypokalemia in 17% (vs. 13%), and hypertension in 22% (vs. 13%), and ALT and AST increase in 12 and 11% of (vs. 5%) patients. For each of these side effects, grade 3–4 rate was ≤5% [85]. In the recently published LATITUDE and STAMPEDE studies, the dose of prednisone was lowered to 5 mg daily, which raised some concerns [6, 7]. Grade 3–4 hypokalemia was, respectively, detected in 10 and 1% patients in the abiraterone arm compared to 1 and <1% patients treated with ADT. This represents a close to fourfold increase when compared to the two mCRPC registration trials that, respectively, described an incidence of grade 3–4 hypokalemia of 2 and 4% [82, 83]. Hypertension was also more common: 37% (all grades) compared to 22% and 10%.

Patients receiving abiraterone should be monitored carefully [86]. Arterial hypertension and hypokalemia should be corrected before initiating treatment. Blood pressure, serum potassium, and symptoms of fluid retention should be measured at least monthly and corrected if required. ALT, AST, and bilirubin levels must be measured prior to starting treatment with abiraterone, and then every 2 weeks for the first 3 months of treatment, and monthly thereafter.

The indication of administering abiraterone should be carefully weighted in the following patients that constitute relative contraindications: patients with a history

of cardiovascular disease or with medical conditions that might be compromised by increases in blood pressure, hypokalemia, or fluid retention and patients taking CYP2D6 substrates with a narrow therapeutic index.

6.2.2.2 Enzalutamide

Enzalutamide is an oral AR receptor antagonist that was specifically engineered to overcome castration resistance in PCa cells harboring AR amplification or overexpression [87]. Enzalutamide has demonstrated significant activity in men with metastatic CRPC before or after chemotherapy [88, 89]. As for abiraterone, enzalutamide is generally very well tolerated and adapted to long-term administration. In the pre-chemotherapy registration trial, Prevail, grade $\geq$ 3 adverse events were recorded in 43% of the patients and 37% of the placebo controls. The most common grade 1–4 side effects were fatigue (36% vs. 26% in control), back pain (27% vs. 22 in control), and constipation (22% vs. 17% in control). There was more hypertension with enzalutamide (13%) than in placebo control (4%). In addition, it should be noted that enzalutamide is a strong inducer of CYP3A4 and a moderate inducer of CYP2C9 and CYP2C19. These combinations can alter the plasma exposure of enzalutamide and should be avoided if possible. Conversely, concomitant use of strong CYP2C8 inhibitors can increase the plasma exposure to enzalutamide.

Enzalutamide belongs to a class of antiandrogens that carries a risk of seizures. This is likely related to inhibition of the γ-aminobutyric acid (GABA)-gated chloride channels by enzalutamide, which lowers the seizure threshold [89]. In the AFFIRM and PREVAIL trials, patients with a history of seizures or with other risk factors for seizures were excluded from trial entry. The risk of seizure was very low <1% in both trials.

Enzalutamide-related fatigue has been the most badly advertised side effect of enzalutamide. Investigators have conducted a pooled analysis across four double-blind, randomized, placebo- or bicalutamide-controlled trials of enzalutamide for mCRPC (AFFIRM, PREVAIL, TERRAIN, and STRIVE), representing 2051 patients in the enzalutamide arms and 1630 in the control arms [90]. Total treatment exposure was longer for enzalutamide (range 219–1294 patient-years) vs. control (range 143–560 patient-years). The unadjusted percentages of men reporting fatigue for all grades were slightly higher in enzalutamide arms (range 28–38% vs. range 20–29%). Grade 3 fatigue AEs were reported by <10% of men and in similar proportions in both arms (1–6% for ENZ vs. 1–7% for control). In all trials, younger men (<75 years) experienced less fatigue vs. older men (20–35% vs. 21–42%, respectively), regardless of treatment. Men, however, should be counseled that fatigue can manifest with enzalutamide administration.

In accordance with the summary of the European public assessment report (EPAR), no specific monitoring is recommended for patients on enzalutamide, except if it is coadministered with warfarin (CYP2C9 substrate), in which case additional INR monitoring should be conducted [91].

The indication of administering enzalutamide should be carefully weighted in the following patients that constitute relative contraindications: patients who had a

seizure, with predisposing factors for seizures, using concomitant medications that may lower the seizure threshold, or patients using CYP3A4, CYP2C9, and CYP2C19 substrates with a narrow therapeutic index [91].

6.3 Side Effects of Targeted Therapies for Renal Cell Carcinoma

The treatment of RCC has been revolutionized by the development since the early 2000s of several therapies targeting the VHL/HIF pathways. These belong to four different classes of drug: tyrosine kinase inhibitors (TKIs), including sunitinib, pazopanib, sorafenib, and axitinib, anti-vascular endothelial growth factor (VEGF) monoclonal antibody bevacizumab, mammalian target of rapamycin (mTOR) inhibitors temsirolimus and everolimus, and finally oral inhibitor of tyrosine kinases MET, VEGFR, AXL, cabozantinib [92–106]. Although most of these drugs have individually demonstrated limited OS benefit, the prognosis for advanced RCC is shifting progressively toward that of a chronic treatable disease (Table 6.4). A result of this is that patients are nowadays treated for increasingly longer periods of time with these agents and usually receive multiple lines of therapy.

Because these drugs belong to specific therapeutic classes, they cause class-specific side effects that have raised new management challenges. Most of their

Table 6.4 Summary of benefit of new targeted agents used in RCC

Drug	Line of treatment (previous treatment)	(*N*) patients	Control arm	PFS (months vs. control)	OS (months vs. control)
IL 2 [107]	1st	255	None	15% ORR	
Temsirolimus [99]	First (poor prognosis)	626	IF	5.5 vs. 3.1	10.9 vs. 7.3
Sunitinib [102, 103]	First	750	IF	11.0 vs. 5.0	26.4 vs. 21.8
Bevacizumab + IF [96, 108]	First	649	IF	10.2 vs. 5.4	23.3 vs. 21.3
Pazopanib [106]	First/second (cytokines)	435	Placebo	9.2 vs. 4.2	22.9 vs. 20.5
Sorafenib [94]	Second (cytokine)	903	Placebo	5.5 vs. 2.8	19.3 vs. 15.9
Everolimus [100, 101]	Second (sorafenib or sunitinib)	410	Placebo	4.9 vs. 1.9	14.8 vs. 14.4
Axitinib [101, 104]	Second (systemic)	723	Sorafenib	6.7 vs. 4.7	20.1 vs. 19.2
Cabozantinib [92, 93]	Second (antiangiogenic)	658	Everolimus	7.4 vs. 3.8	21.4 vs. 15.4

IL-2 interleukin 2; *IF* interferon; *PFS* progression-free survival; *OS* overall survival

side effects are not life-threatening but can severely hamper the quality of life of patients on the long run. Because it is very important to secure long-term compliance to oral drugs, it is critical that side effects are managed preemptively and that patients are correctly informed and educated about the preventive measures. There are many generic side effects associated with TKIs and mTOR inhibitors, including fatigue, hypertension, and diarrhea. In addition, there are several agent-specific side effects: proteinuria with bevacizumab plus IFN, hypothyroidism sunitinib, hand-foot skin reaction (HFSR) most often seen with sorafenib, hepatotoxicity most often seen with pazopanib, and hyperlipidemia most often seen with the mTOR inhibitors [94–97, 99, 100, 102–106]. These side effects and their respective frequency are summarized in Table 6.5. The side effects of cabozantinib, most recently approved, have been treated separately [92, 93].

The impact of side effects can be greatly limited if the patient is well informed and encouraged activating preventive measures. Even mild side effects may have a great impact on a patient's quality of life that may require temporary dose reduction or treatment discontinuation. Physicians should be aware of comorbidities such as diabetes and hypertension that may also increase the risk of certain side effects. To ensure early detection and optimal management of side effects and so maximize patient benefits and compliance, it is important that the physician is aware of the range of manageable side effects associated with each agent and that this information is effectively communicated to the patients.

6.3.1 Life-Threatening Side Effects

In addition to these frequent side effects, potentially life-threatening or lethal adverse events have been reported in the Summary of Product Characteristics of the European Medicines Agency.

- *Sorafenib* has been reported to cause reversible posterior leukoencephalopathy, hypertensive crisis, cardiac ischemia and myocardial infarction, gastrointestinal perforation, and hemorrhage. Preneoplastic skin lesions such as actinic keratosis and keratoacanthomas, but also squamous cell carcinoma, have been reported.
- *Sunitinib* has been reported to cause life-threatening hematologic, cardiovascular, and venous thromboembolic events, pancreatic and hepatobiliary complications, gastrointestinal perforation, and hemorrhage.
- The association of *bevacizumab* + *IFα* has been reported to cause hypertensive encephalopathy, cardiac failure, thromboembolic events, gastrointestinal perforation, and hemorrhage.
- *Pazopanib* has been reported to cause gastrointestinal perforation and gastrointestinal fistula, arterial thrombotic events, hemorrhage, and severe hepatotoxicity.

Table 6.5 Most commonly reported side effects in summary of product characteristics of European Medicines Agency for sorafenib [133], sunitinib [134], pazopanib [135], bevacizumab [136], temsirolimus [137], and everolimus [138]

	TKIs				Anti-VEGF	mTOR inhibitor	
Side Effect	Sorafenib	Sunitinib	Pazopanib	Axitinib	Bevacizumab	Temsirolimus	Everolimus
Gastrointestinal disorders							
Constipation	C	VC		VC	VC		
Diarrhea	VC	VC	VC	VC	VC	VC	VC
Dyspepsia	C	VC		C			
Dry mouth	C	C					C
Flatulence		C	C	C		C	
Glossodynia		VC		C			C
Nausea	VC	VC	VC	VC	VC	VC	VC
Oral pain		C		C		VC	C
Stomatitis	C	VC	C	VC	VC	VC	VC
Vomiting	C	VC	VC	VC	VC	VC	VC
Abdominal pain			VC		C	C	
Gastrointestinal perforation	UC				C	UC	
Acne	C	C				VC	C
Alopecia	VC	C	C	C			C
Dry skin	C	VC		VC	VC		VC
Erythema	VC	C	C	C			C
Hair color changes		VC	VC				
HFSR	VC	VC		VC	C		C
Nail disorder	C	C				VC	VC
Pruritus	VC	C	C	C		VC	
Rash	VC	VC	C	VC		VC	VC
Skin discoloration		VC			VC		
Bacterial and viral infections	UC		UC		C	VC	VC

(continued)

Table 6.5 (continued)

	TKIs				Anti-VEGF	mTOR inhibitor	
Side Effect	Sorafenib	Sunitinib	Pazopanib	Axitinib	Bevacizumab	Temsirolimus	Everolimus
Cough	C	C	C	VC		VC	VC
Dyspnea		C		VC	C	VC	VC
Epistaxis		VC	C	C	C	VC	VC
Pneumonitis	UC	C				C	VC
Pleural effusion						C	
Ejection fraction decreased	C	C	UC	C			
Hemorrhage	VC			VC		VC	VC
Hypertension	C	VC	UC	VC	VC	C	C
Deep vein thrombosis					C		
Thromboembolism					C		C
Supraventricular tachycardia					C		
Pulmonary embolism			UC		C		C
Anorexia	C	VC	C	VC	VC	VC	VC
Hypokalemia					VC	VC	C
Hyperglycemia					VC	VC	VC
Hypercholesterolemia						VC	VC
Hyperlipidemia						VC	VC
Hypophostatemia	VC		C			VC	C
Neutropenia	C	VC	C		VC	C	C
Thrombocytopenia	C	VC	C		VC	VC	VC
Anemia	C	VC			C	VC	VC
Leucopenia	C	C	C		VC	C	C
Lymphopenia	VC	VC				C	C
Creatinine increase	C	C				VC	C
Increase liver enzyme	UC	UC	VC	C		C	C
Proteinuria		UC	C	VC	VC	C	C

Headache	VC	VC	C	VC	C	VC	
Peripheral sensory neuropathy	C	C	UC		VC		
Depression	C	C			C	C	
Intracerebral bleeding						C	
Taste disturbance		VC	VC		VC	VC	
Arthralgia-myalgia	C	VC	C		VC	VC	C
Lacrimation increased		C			VC		
Eyelid edema		C			VC		VC
Conjunctivitis					C		VC
Eyelash discoloration			UC				
Allergic reactions	UC	UC			C		
Fatigue	VC	VC	VC	VC	VC	VC	VC
Hypothyroidism	UC	VC	C	VC			
Hyperthyroidism	UC	UC			VC		
Insomnia		C			VC	VC	VC
Mucosal inflammation		VC	C	VC	C		
Edema		VC	C		VC	VC	VC
Pyrexia						VC	VC

Frequencies are reported as very common (VC; ≥1/10 patients), common (C; ≥1/100 to <1/10 patients), or uncommon (UC; ≥1/1000 to <1/100 patients). Cases are empty if the incidence of the side effect is not reported in Eu SmPC or cannot be estimated from the data available (adapted from reference [109])

- *Axitinib* has been reported to cause gastrointestinal perforation, hemorrhage, arterial thrombotic events, life-threatening hematologic, myocardial infarction, and asthenia.
- *Temsirolimus* has been reported to cause hypersensitivity/infusion reactions, intracerebral bleeding, bowel perforation, pericardial effusion, pneumonitis, renal failure, and delay wound healing.
- *Everolimus* has been reported to cause noninfectious pneumonitis and infections.

6.3.2 Prevention and Management of Most Common Side Effects

6.3.2.1 Dermatologic Side Effects

Early recognition of dermatologic complications is critical, and patients should be taught to report the development of any new skin lesions. *Rash* and *hand-foot skin reaction (HFSR)* are among the most troubling and common side effect of TKIs. Hand-foot skin reaction occurs in ±20% of patients receiving sorafenib and ±30% of patients treated with sunitinib and axitinib. HFSR usually appears after 2–4 weeks of treatment. The onset and severity of HFSR appear to be dose-dependent and often disappear rapidly upon treatment discontinuation. The physiopathology of HFSR is unclear, although it is relatively infrequent with pazopanib. The severity of HFSR can range from minimal skin changes (grade 1) to painful ulcerative dermatitis (grade 3) and often results in dose reduction.

There are no dedicated studies defining the degree of benefit of commonly reported measures for the management of HFSR. Preventive measures for HFSR include removal of any existing hyperkeratosic areas and calluses beforehand [110]. It is important that pressure areas are protected and treated with moisturizing creams or ointments. During treatment, care should be taken to reduce exposure of the hands and feet to hot water and to avoid constrictive footwear, friction, and trauma arising from exercise. Shoes with padded insoles (and possibly also gloves) can be worn. There may be a benefit in sparingly applying moisturizing cream to the hands and feet and educating patients on the first signs of HFSR [111]. Wearing soft and not constrictive shoes and even gloves is recommended. Once it is present, HSFR should be managed with topical application of corticoid-containing cream. Dose reduction, interruption, and event discontinuation may be required for grade 2–3 toxicities.

Management strategies for rash require first differentiating non-serious rash, which is usually moderate and not associated with systemic symptoms, from more severe hypersensitivity reactions such as drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome or Stevens–Johnson syndrome. These are usually associated with mucosal involvement, bullous lesions, and systemic and biological signs. Meticulous skin care, moisturizing cream, and urea-containing lotion are key preventive and therapeutic measures. They require immediate drug discontinuation and specialized dermatologic support.

6.3.2.2 Infections

Everolimus and temsirolimus have dose-dependent immunosuppressive properties and can therefore predispose patients to infections. In the temsirolimus phase III study, infections were reported in 27% of patients (grade 3/4 in 5%) receiving temsirolimus versus 14% in the control arm [99]. In the everolimus phase III study, infections were reported in 13% of patients (grade 3/4 in 4%) versus 2% (grade 3/4 in 0%) in the control arm [100]. Physicians should be aware of this increased risk, and should ensure that any preexisting infections are adequately treated before initiation of mTOR inhibitors. It is particularly important that patients with pulmonary infiltrates or pulmonary symptoms, which are also frequent with mTOR inhibitors, are rigorously assessed for signs of infection, owing to the potential overlap between pulmonary infections and noninfectious pneumonitis.

6.3.2.3 Gastrointestinal Side Effects

Diarrhea

Diarrhea is one of the most common side effects of anticancer therapy. It is not only inconvenient but also potentially life-threatening if not sufficiently managed. There are a number of published clinical guidelines for the management of diarrhea in cancer patients that also apply to targeted therapies in RCC [112]. Patients must be advised to avoid foods that may aggravate diarrhea and favor foods that increase the consistency of stools. In case of persistent diarrhea, it is important to maintain abundant liquid and salt intake, for example, using an WHO solution containing 30 ml (6 level teaspoon) of sugar and 2.5 mL (1/2 level teaspoon) of salt, dissolved into 1 L of water. Loperamide is widely prescribed for anticancer therapy-related diarrhea. For grade 3 or 4 diarrhea, dose adjustments or even discontinuation may be required.

Oral or Upper Gastrointestinal Complications

Oral and upper tract gastrointestinal complications of targeted therapies are very common and include mucositis, stomatitis, dry mouth, and taste loss or disturbance. Mucositis is characterized by painful inflammation and ulceration of the mucous membranes lining the digestive tract, whereas stomatitis more specifically refers to painful inflammation of the mucous lining of the mouth. A meta-analysis by Worthington et al. has evaluated the effectiveness of prophylactic agents for preventing stomatitis in patients receiving chemotherapy [113]. Results from their analysis suggest that amifostine, Chinese medicine (that involved mixtures of 5 or 11 herbs, including honeysuckle flower, licorice root, and magnolia bark), hydrolytic enzymes (pepsin, trypsin, and chymotrypsin or wobe-mugos preparation of enzymes), and ice chips may be beneficial in preventing or reducing the severity of stomatitis. There is consistent evidence from small high-quality studies that red and infrared low-level laser therapy (LLLT) can partly prevent development of cancer therapy-induced oral mucositis. LLLT also significantly reduced pain, severity, and duration of symptoms in patients with cancer therapy-induced oral mucositis [114].

Anorexia and Weight Loss

Anorexia may result as much from a loss of appetite caused by cancer as from treatment-related nausea, vomiting, oral pain, diarrhea, and loss or disturbance of taste. Anorexia-related symptoms, which include weakness, fatigue, depression, tooth loss, and organ damage, can have a negative impact on health-related quality of life, affect a patient's ability to perform daily tasks, and can result in death in severe cases. Pharmacologic intervention may be required in case of severe cachexia; these include megestrol acetate [115], eicosapentaenoic acid diester [116], medroxyprogesterone acetate [117], and mixtures of beta-hydroxy-beta-methylbutyrate, glutamine, and arginine [118].

Gastrointestinal Perforation

Gastrointestinal perforation is a rare but potentially fatal complication that has been reported in association with all the targeted agents except (to date) everolimus. The highest rate is seen with bevacizumab as demonstrated in a meta-analysis of 17 randomized studies, including more than 12,000 patients with various cancers, that reported an overall incidence of gastrointestinal perforation of 0.9% [119]. Risk factors for gastrointestinal perforation include history of past diverticulitis or ulcers, radiation exposure, recent sigmoidoscopy or colonoscopy, gastrointestinal obstruction, and multiple previous surgeries. Gastrointestinal perforation is an indication for immediate discontinuation of anticancer therapy and appropriate treatment of the perforation.

6.3.2.4 Metabolic Toxicities

Fatigue

Fatigue is a persistent, subjective sense of emotional, physical, and/or cognitive tiredness or exhaustion. Fatigue often results from multiple causes. It can be a cancer-related side effect, an adverse event of the treatment, as well as the symptom of other conditions, including hypothyroidism, anemia, depression, sleep disturbances, or pain, that are often seen with targeted therapies [120]. Therefore, any underlying cause of fatigue should first be ruled out before making specific recommendations to the patient. Patients should be encouraged to conserve energy, to reschedule activities to periods of peak energy, and to stay active to promote sleep. Alternatives approaches such as stress management, relaxation techniques, and nutritional support maybe useful [121].

Hypothyroidism

Hypothyroidism is a very common side effect of sunitinib. Preexisting hypothyroidism should be detected and treated before starting sunitinib treatment, as recommended in the EU SmPC. There is no consensus on the frequency of thyroid function monitoring under treatment, although initially monthly TSH dosage are advisable [122]. It is not clear whether these recommendations for thyroid function monitoring should be extended to all patients treated with TKIs.

Hyperglycemia

Hyperglycemia is a very common side effect of the mTOR inhibitors temsirolimus and everolimus [99, 100]. It is recommended to monitor fasting serum glucose before initiating treatment with everolimus or temsirolimus and periodically thereafter. Hyperglycemia should be treated with dietary modifications and an increase in the dose or initiation of insulin and/or hypoglycemic agent therapy.

6.3.2.5 Cardiovascular Side Effects

Hypertension

Arterial hypertension is a common side effect of inhibitors of the VEGF pathway, reported at a frequency of between 12 and 41% in patients treated with sorafenib, sunitinib, bevacizumab + IFN-a, or pazopanib. Management of angiogenesis inhibitor-related hypertension should follow the recommendations of the European Society of Hypertension. Blood pressure (BP) monitoring is mandatory before and during therapy; however, there is general disagreement about when and how BP should be measured [109, 123, 124]. The routine use of home BP monitoring may be valuable in standard care for early detection and accurate assessment of BP changes [123, 124]. Home monitoring can be recommended, but then patients need to be provided with individualized thresholds for contacting their physician. When diagnosed, hypertension should be treated with standard antihypertensive therapy with a preference for angiotensin-converting enzyme (ACE) and inhibitors and angiotensin II receptor blockers (ARBs).

Cardiovascular Events

Initiation of TKIs and inhibitor of the VEGF pathway requires careful monitoring of cardiac effects. Generally, VEGF-targeted agents should be used with caution in any patients with clinically significant cardiovascular disease or preexisting congestive heart failure, and these patients should be closely monitored for clinical signs of heart failure. Periodic measurements of LVEF using echocardiography or magnetic resonance imaging are the recommended methods for monitoring cardiac function during cancer treatment [125–127]. Since cardiac dysfunction can be hampered by other side effects such as hypothyroidism or hypertension, these conditions should be carefully monitored and managed. Except for few anecdotal cases, it is not known whether left ventricular dysfunction is reversible upon treatment cessation.

Venous and Arterial Thromboembolism

Venous thromboembolism (VTE) is a common complication in cancer patients [128, 129]. Risk factors include age older than 65 years, previous VTE events, and surgery. It is not clear whether targeted agents increased the risk of VTE. Although the EU SmPC for bevacizumab does not mention VTE as a side effect, a meta-analysis of 15 studies investigating the treatment of various solid tumors with bevacizumab suggested an increased incidence of VTE, 12% for all grades and 6% for high grade [130]. General recommendations on the prophylaxis and treatment of thrombosis in cancer patients have been produced by ASCO and the American

College of Chest Physician [131]. Anticoagulation prophylaxis is not recommended for ambulatory patients with cancer receiving systemic treatment; whether the increased risk of thrombotic events with some targeted agents warrants prophylaxis in ambulatory patients remains unclear. Especially, acetylsalicylic acid or other antiplatelet drugs should be used with caution in association with anti-VEGF agents because of the increased risk of bleeding.

6.3.2.6 Wound Healing and Hemorrhage

Wound healing is one of the most important challenges that surgeons face when confronted with RCC patients treated with targeted therapies. Targeted agents have a variety of half-life, with temsirolimus at 17 h, sorafenib at 1–2 days, sunitinib at 4 days, and bevacizumab at 17 days. To minimize the effect on wound healing, most series have advocated at least a 2-week washout period for most oral TKIs. This has been especially well documented with bevacizumab so that the EU SmPC includes a black box warning recommending treatment discontinuation for at least 28 days in case of surgery. Signs of wound dehiscence or infection should be regularly monitored. TKIs and mTOR inhibitors may also impair wound healing, although clear data and recommendations on the minimal duration of treatment interruption before or after surgery are still lacking, with suggestions ranging from 7 to 14 days. Of note, one study with TKIs found that in RCC patients undergoing cytoreductive nephrectomy or resection of retroperitoneal recurrence, rates of incision-related complications were similar between patients treated with preoperative sorafenib, sunitinib, or bevacizumab and those who underwent up-front surgery [132].

Minor hemorrhagic events such as epistaxis are common in patients treated with bevacizumab, sunitinib, temsirolimus, and everolimus. The impact of minor bleeding events can be limited by good patient education. In contrast, severe life-threatening events are more exceptional, mostly occurring with bevacizumab. However, it has raised the concern of treating patients' metastases of the central nervous system (CNS) with bevacizumab + IFN-a. These patients were excluded from the registration trial. TKIs sorafenib and sunitinib can be safely administered to patients with CNS metastases that have been irradiated. One of the primary measures against bleeding is an optimal control of blood pressure to avoid hypertension.

6.3.3 Toxicity of Cabozantinib

In RCC population, the experience in the safety profile of cabozantinib is limited to the results of one phase III trials [92, 93]. In the phase III METEOR trial, common AEs included diarrhea, fatigue, nausea, decreased appetite, hand–foot syndrome, and hypertension, which are also observed with other VEGFR TKIs in patients with RCC. Dose reductions occurred more frequently with cabozantinib than with everolimus (among 60% and 25%, respectively), underlining the need for careful AEs monitoring. We thus believe that the aforementioned recommendations may apply.

6.4 Summary

The unique sensitivity of prostate cancer to hormone therapy and of kidney cancer to therapies targeting the VHL/HIF pathways is creating a unique therapeutic portfolio, which does not include chemotherapy. These classes of drugs share the particularities of having to be prescribed for extended periods of time because they don't eradicate the disease but rather switch it to a more chronic state. Emerging therapies generate the hope of multiple sequential treatments that will effectively prolong the duration of life. Most of their side effects are more bothersome than really morbid, but because these drugs are administered chronically, it may result in profound alteration of the patients' quality of life. Ultimately, this is a threat to compliance and a danger hampering the chronic efficacy of these treatments. In addition, the side effects of many of these drugs often overlap with common, widespread chronic illnesses such as diabetes, hypertension, hypercholesterolemia, and heart failure. Therefore, the management of these side effects is of utmost complexity, so that only a multidisciplinary preventive approach involving physicians, nurses, and properly educated patients will guarantee an optimal efficacy.

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Central Nervous System

7

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Abstract

Primary central nervous system tumors (CNS) make up for a heterogeneous group of neoplasms for clinical and biological behavior. The causes remain to be defined. Inherited predisposition to glioma is suggested by a number of rare inherited cancer syndromes, such as Turcot's and Li–Fraumeni syndromes and neurofibromatosis, which however, even collectively, account for <5% of glioma cases. CNS tumors differ in many ways from other tumors. First, these tumors are separated by an important natural barrier, the blood–brain barrier, with the aim of defending the CNS from external noxa but, in the case of cancer, limiting the efficacy of therapy. Second, the tumors of the CNS are malignant not only because of their biological behavior but because of their localization. Even very

This is an updated version of the chapter contributed by Miriame Mino, Krisztian Homicsko, and Roger Stupp for book *Side Effects of Medical Cancer Therapy* in 2013. The updates in this chapter were solely done by Patrizia Farina, Florian Scotté, Chiara Villa, Bertrand Baussart, and Anna Luisa Di Stefano.

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M. A. Dicato, E. Van Cutsem (eds.), *Side Effects of Medical Cancer Therapy*,
https://doi.org/10.1007/978-3-319-70253-7_7

small and slow-growing tumors localized at important regions of the brain, like the brain stem, can have serious, deleterious, and fatal impact. Finally, tumors of the CNS have a direct impact on the quality of life of patients, with long-term disabling effects on everyday life. Therefore, tumors of the CNS require early diagnosis and a rapid multidisciplinary approach to choose optimal treatment. In these cases, special attention must be taken to select chemotherapies and targeting agents that do cross the blood–brain barrier.

The focus of this chapter is side effects from chemotherapies used to treat a wide variety of tumors, from gliomas to metastatic (meningeal disease) lesions from other organs. This chapter will discuss main complications from the treatment of CNS disease (glioma, medulloblastoma, and carcinomatous meningitis), specifically from radiotherapy, from cytotoxic, from targeted anticancer therapy, from immunotherapy, and from supportive care measures.

Keywords

CNS · Glioma · Temozolomide · Bevacizumab · Immunotherapy · Blood–brain barrier

7.1 Introduction

The focus of this chapter is on side effects of treatments for primary tumors of the central nervous system (CNS) and on particularities of supportive care for tumor manifestations in the CNS. For the management of secondary (metastatic) tumor manifestations in the CNS, the reader should also refer to the respective chapters of the primary tumor of origin. Generally, brain metastases will respond in a similar manner to chemotherapy than other systemic disease, provided the agent crosses the blood–brain barrier and sufficient drug concentrations in the CNS can be achieved. This chapter will be mainly focused on gliomas which correspond to most common malignant brain tumor in adults.

7.2 Gliomas: Epidemiology, Classification, and Management Issues

Gliomas account for 30% of all primary brain tumors and are responsible for around 13,000 cancer-related deaths in the USA each year. Newly diagnosed gliomas are estimated around 20,000 in the USA and 2500–3000 in France per year. For the past century, the classification of brain tumors has been based largely on concepts of histogenesis that tumors can be classified according to their microscopic similarities with different putative cells of origin and their presumed levels of differentiation. However, research into molecular biology of the last two decades proved that a number of somatic molecular alterations can better define biological entities and clinical aggressiveness. Basing on those achievements, the WHO

(World Health Organization) recently updated the classification of gliomas [1] and stated that two of them—the isocitrate dehydrogenase (*IDH*) mutations and chromosome 1p/19q codeletion—are determinant for a so-called "integrated" diagnosis, irrespective of morphological similarities of tumor cells to putative progenitors. By now, diffuse gliomas are broadly separated according to two main dichotomies:

- *IDH* mutations) principally differentiate the more indolent low-grade gliomas (grade II and grade III and progressive glioblastoma) from primary glioblastoma, the most aggressive of gliomas.
- 1p/19q Codeletion, which is tightly associated with *IDH* mutations), specifically tags oligodendrogliomas among lower grades.

Isocitrate dehydrogenase is an enzyme with three isoforms, i.e., *IDH1*, *IDH2*, and *IDH3* [2]. Intracellularly, it catalyzes the oxidative decarboxylation of isocitrate to α-ketoglutarate (α-KG). *IDH* mutations) harbor in specific cancer entities: in gliomas (70–90% of low-grade gliomas and secondary glioblastoma), in hematological malignancies (~20% of acute myeloid leukemia), and in intrahepatic cholangiocarcinoma, chondrosarcoma, and melanoma [3]. *IDH* mutation) is one of the earliest known genetic events in low-grade gliomas; it is thought to be a "driver" mutation for tumorigenesis probably by accumulation of the onco-metabolite 2-hydroxyglutarate (2 HG). At a prognostic level, *IDH* mutations) have revealed to have a major prognostic impact on morphological stratification based on the WHO's 2007 glioma grades, depicting a more favorable prognosis in *IDH* mutants) compared to tumors with wild-type *IDH*)in all glioma grades and recognizing a worse outcome common to the group of *IDH*)wild-type gliomas independent of their grading [4].

Chromosome 1p/19q codeletion is strongly associated with classical oligodendroglial features. It results from an unbalanced translocation between the entire arm of 19q and 1p. At the genomic level, it corresponds to a complete loss of the 1p and 19q arms, which is important to distinguish from 1p partial distal deletions (typically 1p36) that occur in astrocytic tumors and are associated with a poor prognosis [5–7]. 1p/19q Codeletion is a strong favorable prognostic factor, and since 1998 it has been associated with response and benefit to adjuvant chemotherapy with procarbazine, CCNU, and vincristine (PCV) after radiotherapy in anaplastic oligodendrogliomas [8].

The reasons for this better prognosis are yet to be determined.

These two principal genetic alterations are linked to each other: 1p/19q codeleted gliomas are systematically associated with *IDH1* or *IDH2* mutations.

For the simplified algorithm of the new integrated classification of gliomas basing of *IDH* and 1p/19q status, the reader can refer to the original article by WHO 2016 [1].

New entities for diffuse gliomas by now correspond to diffuse astrocytoma *IDH* mutant, diffuse astrocytoma *IDH*) wild-type, anaplastic astrocytoma *IDH*) mutant, anaplastic astrocytoma *IDH* wild-type, glioblastoma *IDH* mutant), glioblastoma

IDH wild-type, and oligodendroglioma and anaplastic oligodendroglioma which harbor according to this last definition *IDH*)mutations and 1p/19q codeletion. According to a recent reclassification of diffuse gliomas by the POLA French network, the 2016 WHO classification proved to be highly accurate in predicting survival, confirming the value of adding molecular characteristics [9]. The best prognosis is observed in anaplastic oligodendroglioma *IDH* mutant) 1p/19q codeleted (median survival 211.2 months), the worst prognosis is observed in *IDH* wild-type gliomas (median survival 20 months), and an intermediate prognosis is observed in *IDH* mutant) 1p/19q intact gliomas (median survival 103.9 months). Interestingly, among the groups of *IDH*)wild-type gliomas and *IDH* mutant 1p/19q intact gliomas, the grade does not impact survival, and no difference is observed between grade III and grade IV.

According to this last updated classification, adult patients with a good Karnofsky Performance Status score (KPS ≥70) and younger than 65 years old should be treated according to the two following standard: Stupp concomitant radiochemotherapy followed by adjuvant chemotherapy with temozolomide for newly diagnosed glioblastoma [13] and RT followed by adjuvant PCV chemotherapy for newly diagnosed anaplastic oligodendroglioma [8].

Regarding IDH mutant anaplastic astrocytoma [1] and high-risk low-grade gliomas, those ones have been showed to benefit from procarbazine, lomustine, and vincristine following RT in two recent phase III randomized trials so far [8, 10].

In elderly patients (≥65) with glioblastoma and good performance status (KPS ≥70), the addition of temozolomide to short-course radiotherapy 40 Gy in 15 fractions proved to result in longer survival than short-course radiotherapy alone in a recent phase III trial [10].

Finally for patients with a poor performance status, specifically if elderly and with KPS >70, temozolomide in monotherapy could be also proposed since it was proved to be associated with improvement of functional status and increased survival compared with supportive care alone, especially in patients with methylated MGMT promoter [11]. At recurrence, a number of options can be discussed including second-line chemotherapy with antiangiogenic drugs, nitrosoureas, carboplatin, and target therapies.

7.3 Therapeutical Approaches

Therapeutical issues in management of gliomas are given by their infiltrative nature and their localization and diffusion to functional CNS regions, making a complete resection challenging and microscopically not achievable and natural history affected by high mortality and morbidity by both tumor progression and treatments' side effects. Even after macroscopic gross total resection, gliomas virtually always recur. Thus, additional therapy with radiation and/or chemotherapy is indicated with a timing that depends on histological grading.

7.4 Surgical Treatment

The surgical approach must be individualized for each patient. Primary goals correspond with:

- Establishing diagnosis
- Maintaining the patient's preoperative KPS and minimizing morbidity
- Maximizing survival in good clinical conditions by potentiating anticancer treatments
- Improving tolerance to brain irradiation
- Permitting access to clinical trials and targeted therapies

When tumor debulking is not indicated or cannot be ruled out, needle biopsy is one of the least invasive ways of obtaining tissue for pathological diagnosis. This procedure is usually reserved for patients with multiple comorbidities who could not be able to tolerate a large cranial surgery or for those with unresectable tumors due to its location.

However serious side effect of needle biopsy such as intracranial hemorrhage should be taken into account (2%).

Surgical approach is established basing on histological diagnosis, age, and more recently even prognostic and predictive molecular features such as the *IDH* mutational status of the tumor. Those combined elements permit to define goals of surgery together with anticancer treatment by basing on life expectancy.

IDH-mutated low-grade gliomas and 1p/19 codeleted gliomas are slow-proliferating tumors with median survival accounting for 12.5 years and 17.6 years, respectively [12], and are relatively sensitive to radiotherapy and chemotherapy allowing a long-term disease control. In this setting, total and supra-total resections have been proven to sensitively impact time to relapse and survival. Thus, given the relative long-life expectancy of these patients, the main goal of neurosurgery in these tumor subgroups is the largest resection when feasible by taking into account motor transient neurological postoperative deficits.

Awake surgery allows to increase safety, precision, and removal success when glioma is located near eloquent cortex in areas that include, but not limited to, the precentral gyrus (motor strip), corticospinal tracts, Broca's speech area, and Wernicke's speech area.

Inversely *IDH* wild-type gliomas and notably glioblastomas features correspond to higher infiltration of surrounding parenchyma and also a poorer prognosis with a median time to recurrence of around 9 months and overall survival of 19 months. In this setting, complete removal is a good prognostic factor and is recommend when feasible; however, n eurosurgical approach is less aggressive basing on the shorter survival expected for patients and the risk of neurological deficits affecting the quality of life.

7.5 Radiotherapy

Historically, radiotherapy has been the sole treatment of malignancies in the brain. The radiation fields, the dose, and the fractionation vary from precise stereotaxic irradiation (radiosurgery) to focal or whole brain radiotherapy. The primary determinants of toxicity are the administered cumulative dose, the dose of individual fractions, and the irradiated volume. Vulnerability and radiosensitivity differ between the various structures of the CNS. Fractionated radiotherapy with concurrent and adjuvant temozolomide is the standard of care after biopsy or resection of newly diagnosed glioblastoma in patients up to 65 years of age [13]. Hypofractionated radiotherapy for elderly patients with fair to good performance status is appropriate, and recently the addiction of concurrent and adjuvant temozolomide to hypofractionated radiotherapy seems to be safe and efficacious without impairing quality of life for elderly patients with good performance status [14].

In high-grade glioma, focal radiotherapy to the tumor with a safety margin of 1.5–2 cm up to a total dose of approximately 60 Gy in 1.8 to 2 Gy fractions is commonly delivered. At doses above 60 Gy, the risk of long-term damage to the normal brain tissue increases exponentially, with no increase in efficacy. For low-grade glioma doses of 50 Gy suffice. Focal reirradiation represents an option for select patients with recurrent glioblastoma, although this is not supported by prospective randomized evidence.

Main side effects can be divided into reversible short-term and irreversible long-term toxicity (Tables 7.1 and 7.2). Acute side effects are hair loss (may persist), fatigue, somnolence, and nausea and vomiting. Since radiotherapy induces inflammation, the tumor- and mass effect-related symptoms like headaches, nausea and vomiting, and neurologic symptoms may temporarily increase during radiotherapy. The practice of routine prophylactic steroid administration during cranial

Table 7.1 The most commonly used agents in CNS tumors

Temozolomide
Nitrosoureas
Carmustine (BCNU)
Lomustine (CCNU)
Fotemustine
Nimustine (ACNU)
Procarbazine
Vincristine
Bevacizumab
Ifosfamide
Carboplatin
Etoposide
Cytarabine
Methotrexate
Thiotepa

Table 7.2 Side effects of radiotherapy after brain or spinal cord irradiation

Time after irradiation	Symptoms
Brain	
Acute (days)	Increased ICP, nausea, and vomiting
Early delayed (weeks)	Somnolence syndrome, fatigue, hair loss, symptoms of tumor recurrence
Delayed (months–years)	
(a) Necrosis	Dementia, symptoms of tumor recurrence
(b) Leukoencephalopathy	Dementia or asymptomatic
Spinal cord	
Early delayed (weeks)	Lhermitte's sign
Delayed (months–years)	
(a) Necrosis	Transverse myelopathy
(b) Hemorrhage	Acute myelopathy
(c) Motor neuron disease	Flaccid paraparesis, amyotrophy
(d) Arachnoiditis	Asymptomatic
(e) SMART syndrome	SMART syndrome: stroke-like migraine attacks after radiation therapy

irradiation has been abandoned, and steroids should be introduced in case of symptoms only. The major long-term side effect of irradiation of the brain is leukoencephalopathy, which is due to destruction of the myelin sheaths covering nerve fibers. The symptoms are greatly variable, from a frequent pure radiologic finding without clinical symptoms to mild confusion and cognitive impairment to progressive invalidating dementia and functional deficits. Factors that contribute to the development of neurocognitive deficiency include volume of irradiation, patient's age (brains of older patients are more vulnerable), tumor volume and localization, and genetic factors [15]. Because of the developing brain, children below the age of 3 years are particularly sensitive to radiotherapy. In adults, 26% of patients develop leukoencephalopathy as early as 3 months after the end of whole brain radiotherapy. Preexisting leukoaraiosis seems to be a major determinant of long-term damage [16].

It is not uncommon to observe increased contrast-enhancement and surrounding T2/FLAIR (fluid-attenuated inversion recovery) hyperintensity *within the radiation treatment field* on this scan compared to the prechemoradiation scan. While these radiographic findings raise the possibility of tumor progression, they may also reflect the biologic effect of chemoradiation on the tumor and the tumor microenvironment, typically referred to as "treatment effect" or tumor "pseudoprogression." Pseudoprogression has been reported to occur predominantly (in almost 60% of cases) within the first 3 months after completing treatment, but it may occur from the first few weeks to 6 months after treatment. Pseudoprogression and

pseudoresponse are abnormalities that have been described following high-grade tumor treatment, and remarkably both appear to be associated with future favorable patient outcome. Both phenomena appear to be best diagnosed through follow-up RM. FDG-PET can help in analysis of areas of radiation injury and residual/recurrent brain tumors.

Finally, a number of late delayed acute neurological syndromes after brain irradiation have also been reported in long survivors also associating transient contrast-enhancement lesions on MR that could be also misinterpreted as tumor progression. Neurological peculiar symptoms can be headache and signs of unilateral hemispheric dysfunction for the SMART syndrome (stroke-like migraine attacks after radiation therapy) [17], PIPG for abrupt partial seizure activity [18], and ALERT syndrome for patients presenting with encephalopathy [19]. Despite described separately, these syndromes actually share several core characteristics such as the long interval from brain irradiation, the acute paroxysmal onset, and the eventual association with transient enhancing MR abnormalities, reversibility, and recurrence suggesting that they share a common pathological substrate [20].

7.6 Chemotherapy

The blood–brain barrier, although often partially disrupted at the site of the tumor, is an obstacle to delivery of adequate concentrations of chemotherapy to the brain. The most commonly used agents in the treatment of primary CNS tumors are summarized in Table 7.1.

Drug therapy is used alone, as single agent, or in combination regimens and concomitant with radiotherapy. In the following sections, the most commonly used agents are discussed, with specific focus on dosing and toxicity when used for the treatment of brain tumors and CNS disease.

7.7 Agents Commonly Used Against Glioma

7.7.1 Temozolomide (EU, Temodal; USA, Temodar)

Temozolomide (TMZ), an alkylating cytotoxic agent, is nowadays the most commonly used drug in the treatment of malignant glioma [21]. It is used in a variety of different dosages and regimens, usually either as a single agent or in combination with concomitant radiotherapy (Table 7.3 and Fig. 7.1) [22]. Since it is rapidly absorbed in the gut with almost 100% bioavailability, oral formulation is possible and permits ease of administration and dosing. It readily crosses the blood–brain barrier, allowing for cytotoxic tumor tissue concentrations.

TMZ is usually well tolerated. Gastrointestinal intolerance is the most common side effect, while myelosuppression is dose limiting. The severity of the observed toxicities is variable, and the incidence depends on the dosing regimen. For the

Table 7.3 Dosing regimens of TMZ

Schedule	Dose (mg/m^2)	Dose intensity (mg/m^2/week)	References
Daily for 5 days, repeat every 28 days	150–200	250	Initially an approved standard dosing
Daily for 42–49 days	75	315	Brock et al. approved in conjunction [23] with radiotherapy (Stupp et al. [13])
Daily continuously nonstop (metronomic)	50	350	Perry et al. [24]
Daily for 7 days, repeat every 14 days	100–150	525	Tolcher et al. [25]
Daily for 21 days, every 28 days	75–100	525	Tolcher et al. [25]

scheme of intermittent, once a day for 5 consecutive days administration, antiemetic prophylaxis is almost always required. Continuous low-dose regimen often does not require any antiemetic drug beyond the first 2–3 days of administration. Profound lymphocytopenia, on the other hand, is commonly observed with continuous dosing, while late thrombocytopenia is more frequent with the intermittent regimen [26].

Table 7.4 presents the common side effects of TMZ, all grades, compared to radiotherapy.

7.7.1.1 Hematologic

Myelosuppression, in particular late occurrence (>21 days after treatment start) thrombocytopenia, is a side effect of TMZ.

During chemoradiotherapy, TMZ is given at a daily (7/7d) dose of 75 mg/m^2, approximately, 1–2 h before irradiation (including weekends and days without radiotherapy), starting simultaneously with the first day of radiotherapy until the last day of irradiation, which is usually 30 fractions over 40–49 days max [28]. Complete blood counts are to be performed weekly. Although myelosuppression is a dose-limiting toxicity of most cytotoxic chemotherapies, a reported benefit of TMZ is that myelosuppression is relatively uncommon. Most studies report an overall incidence of 5–8% for grade 3/4 myelotoxicity.

Low blood counts may occur several weeks after the end of chemoradiotherapy (continue to monitor CBC). When the platelet count drops below 75×10^9/L (grade 2) or the neutrophil count is $<1 \times 10^9$/L (grade 3), chemotherapy should be temporarily suspended. It can be restarted once the values have recovered (neutrophils >1.5, thrombocytes >100, or toxicity grade <2). Occurrence of toxicity during concomitant chemoradiotherapy is not a reason for not proceeding with standard adjuvant/maintenance chemotherapy after the end of the chemoradiotherapy [29].

With the standard 5-day, daily dosing regimen, the nadir commonly occurs after 3 weeks (days 21–28). During initial treatment cycles, blood counts should be checked on day 22 and day 29 (=day 1 of the subsequent cycle). Occasionally,

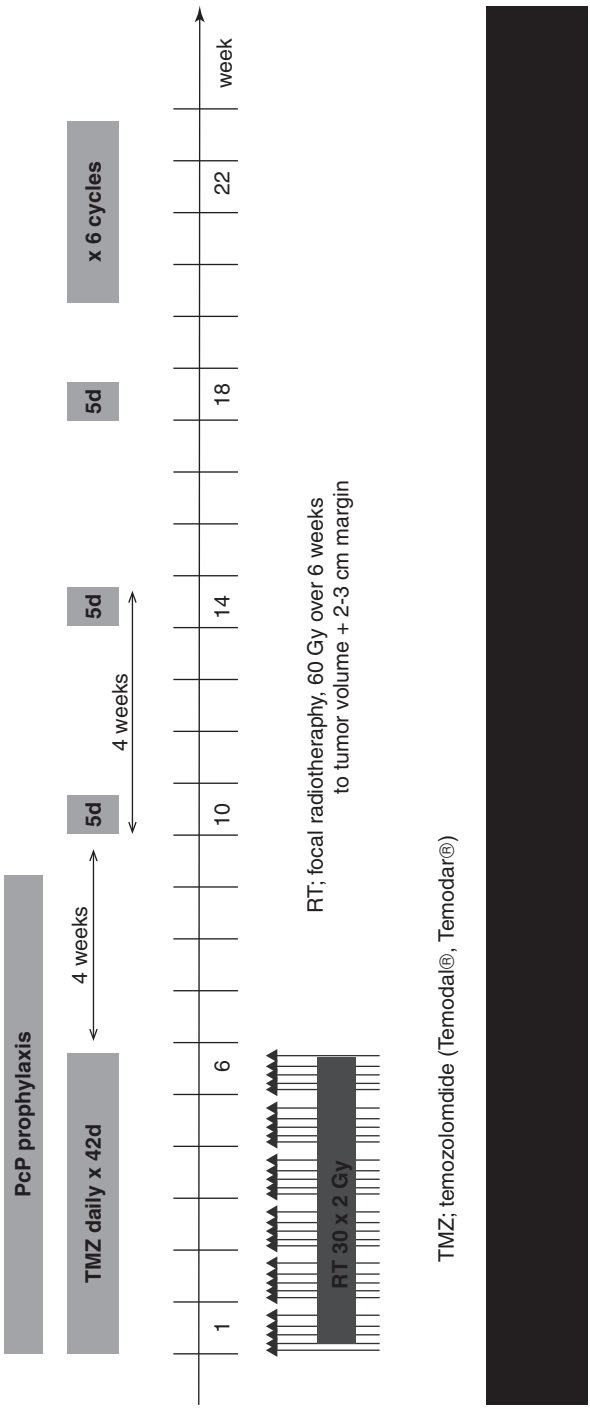

Fig. 7.1 Standard-of-care radiochemotherapy regimen. *TMZ* temozolomide (Temodal®, Temodar®)

Table 7.4 Common side effects of temozolomide (TMZ), all grades, compared to radiotherapy (RT) only

	RT alone (%)	RT + TMZ (%)	Comment/treatment/prevention
Nausea	16	36	5-HT3 agonist, domperidone, or metoclopramide, 30 min before TMZ. Take caps on an empty stomach. Eat small, frequent meals
Vomiting	6	20	See above
Constipation	6	18	Laxatives; drink well; exercise, if possible
Headache	17	19	Painkillers
Fatigue	49	54	Rest
Convulsions	7	6	Optimize antiepileptic treatment. Interactions with TMZ and some antiepileptic drugs
Anorexia	9	19	
Skin rash	15	19	Avoid sun exposure, especially when undergoing RT
Alopecia	63	69	RT, not TMZ, will induce alopecia
Infection	5	9	
Leukopenia/ neutropenia	6	9	See paragraph on hematotoxicity
Thrombocytopenia	1	4	See paragraph on hematotoxicity

Table created with data from Cohen et al. [27]

patients require an additional delay of 3–14 days until blood counts recover. In case of severe myelosuppression (e.g., ≥grade 3 or delayed recovery), dose reduction by 50 mg/m^2 is recommended. In case of hematologic toxicity during chemoradiotherapy, prudence is advised when dosing the initial cycle of subsequent adjuvant therapy (dose for cycle 1: 150 mg/m^2/day for 5 days, to be escalated in the absence of significant hematologic toxicity to 200 mg/m^2).

Profound lymphocytopenia occurs frequently with the continuous TMZ regimen (e.g., during concomitant chemoradiotherapy) and may be further enhanced by the frequent administration of corticosteroids. These patients are at risk for *Pneumocystis jirovecii* pneumonia (PCP, formerly known as *Pneumocystis carinii*), and primary prophylaxis should be considered (Table 7.5). Other complications associated with an immunosuppressed state are reactivation of herpes zoster infection, exacerbation of chronic hepatitis, and Kaposi's sarcoma.

7.7.1.2 Gastrointestinal

One of the most common side effects of TMZ is mild to moderate nausea and occasional vomiting that can be prevented by a low-dose prophylactic administration of 5-HT3 inhibitors (e.g., lower-dose ondansetron, 4 mg; granisetron, 1 mg) or metoclopramide in almost all patients. Because 5-HT3 antagonists are associated with their own toxicity, like constipation and headache, chronic repeated dosing is to be

Table 7.5 Prophylaxis of *Pneumocystis* pneumonia

Agent	Dose and frequency	Remarks
Pentacarinat (pentamidine)	300 mg inhalation, every 4 weeks	In the authors' experience the preferred regimen
Trimethoprim-sulfamethoxazole (bactrim, septra)	1 double-strength (160/800 mg) tablet 3×/week (Monday, Wednesday, Friday)	Cave myelosuppression with sulfa drugs
Dapsone (dapsone)	100 mg 1×/day	If intolerance to TMP-SMX

A high frequency of opportunistic infections was observed in the first trials using the continuous low-dose TMZ regimen [26], and a primary prophylaxis was introduced for subsequent clinical trials. The manufacturer's recommendation is primary prophylaxis during TMZ/RT (see Temodal/Temodar package insert). Alternatively, some institutions follow on a regular basis the total lymphocyte and CD4-positive lymphocyte count, and prophylaxis is proposed if the CD4 value is less than 200–250/mm^3 or the total lymphocyte count is <500 mm^3. Commonly recommended prophylactic regimens are as follows

avoided. In the authors' experience, a low dosage of the 5-HT3 antagonist during the first 2–5 days of a cycle is usually sufficient. With the continuous TMZ dosing regimens, a simple antiemetic prophylaxis with metoclopramide or domperidone will commonly suffice, and up to half of the patients may not need any antiemetic treatment beyond the first days of treatment.

7.7.1.3 Alopecia

TMZ does not induce alopecia; however, radiotherapy will. It can be partial or complete and is seen in up to 63% of patients after radiochemotherapy.

7.7.1.4 Infection (Oral Thrush, Wound Infection, Herpes Simplex)

Immunosuppression (e.g., lymphocytopenia) induced by chronic TMZ administration (and often exacerbated by concomitant corticosteroids) will lead to oral candidemia, herpes reactivation, or wound infection. Other than consideration of PCP prophylaxis (as described earlier), prophylactic antibiotic therapy is not recommended.

7.7.1.5 Neurologic and Psychiatric

Side effects such as anxiety, sleeping disorder, emotional instability, drowsiness, dizziness, confusion, memory loss, blurred vision, and concentration difficulties have been observed. These side effects may be partly caused by TMZ, but they have also been observed in patients treated by radiotherapy only and may be explained by the tumor itself or the frequent corticosteroid administration.

Rarely, neurological complication by herpes simplex encephalitis after concomitant radiochemotherapy with temozolomide has been reported in patients with high-grade glioma [30].

In this setting diagnosis could be challenging due to the confounding clinical presentation and the atypical biological findings. Prognosis is poor, with high short-term mortality and severe residual disability in survivors.

7.7.2 Nitrosoureas (Lomustine, Carmustine, Nimustine, and Fotemustine)

Before the widespread utilization of TMZ alone and concomitant with radiotherapy, the combination of procarbazine, lomustine (CCNU), and vincristine (known as the PCV regimen) has been used since the 1980s [31]. Due to ease of administration and overall excellent tolerance, TMZ has largely replaced the PCV regimen; superiority of either treatment has never been formally investigated. The PCV regimen requires intravenous administration of vincristine, and the regimen is associated with a high incidence of myelosuppression, occasional infections, and frequent treatment delays.

Lomustine (CCNU), carmustine (BCNU), nimustine (ACNU), and fotemustine are alkylating nitrosourea anticancer cytotoxic drugs [32]. They produce DNA and RNA alkylation. They are greatly soluble in lipids, which allows their passage through the blood–brain barrier. The main toxicities are hematologic and gastrointestinal. Myelosuppression is the dose-limiting side effect. Lomustine is the drug most commonly used for glioma therapy and is one of the components of the PCV regimen (Table 7.6). ACNU and fotemustine are used occasionally in some countries such as Germany and Japan (ACNU) and France and Italy (fotemustine). Carmustine was for long the standard of care in the USA [33]. As a single agent the

Table 7.6 The PCV regimen

Agent	Dose (mg/m^2)	Days of administration
Modified PCV		
Procarbazine	60	8–21
CCNU	110	1
Vincristine	1.4	8, 29
British PCV		
Procarbazine	100	1–10
CCNU	110	1
Vincristine	1.5	1

The PCV regimen was developed in the late 1970s [34], aiming at a non-cross-resistant combination of three agents with activity against brain tumors. For vincristine, antitumor activity was assumed based on the neurologic toxicity induced by this agent. For over 20 years, this regimen was considered the most active treatment against malignant glioma and used in many large clinical trials. Unfortunately, a sufficient antitumor activity as adjuvant treatment in newly diagnosed glioma patients could never be established, albeit that antitumor activity was demonstrated in subgroup analyses. One reason for failure may have been the substantial toxicity, in particular the overlapping hematotoxicity induced by these agents, which led to frequent delays, early treatment discontinuations, or fatal complications. Several modifications and variations of the regimen exist

standard dose of lomustine is 130 mg/m^2; however, in combination and in patients having received prior chemotherapy, only a reduced dose of 90–110 mg/m^2 can be tolerated. It is given by mouth once every 6–8 weeks.

7.7.2.1 Myelosuppression

The myelosuppression is dose dependent and cumulative and occurs late in the treatment cycle (nadir fifth week, occasionally even later). Thrombocytopenia observed around day 28 is often followed by neutropenia occurring after day 35. The leukopenia can persist up to 2–3 months after the end of the treatment.

7.7.2.2 Gastrointestinal System

Frequency of side effects is variable. Nausea and vomiting most often appears 4–6 h after administration and may persist for 24–48 h, associated with anorexia for 2–3 days. Antiemetic treatment usually has a good effect on nausea. Mild and clinically nonsignificant elevation of liver function tests is often observed. Stomatitis and diarrhea are often seen.

7.7.2.3 Neurologic System

When combining lomustine with other drugs, neurologic side effects such as apathy, confusion, stuttering, and disorientation have, in rare cases, been described.

7.7.2.4 Respiratory System

One of the limitations of nitrosourea therapy is idiopathic pulmonary fibrosis, most commonly seen with carmustine. Moderate to severe respiratory insufficiency is thus a relative contraindication to the treatment with nitrosoureas. If pulmonary symptoms occur, presenting often with a diffuse infiltrate, and once other causes have been ruled out, treatment is a prolonged course of corticosteroids [35].

7.7.3 Procarbazine

Procarbazine is another alkylating agent causing DNA cross-links followed by DNA breaks. Myelosuppression is the main side effect, with neutropenia and thrombocytopenia being dose limiting. Nausea and vomiting are common. Within the PCV regimen, the dosage is 60 mg/m^2 daily PO for 14 days (day 8–21); as a single agent, doses of 100–150 mg/m^2 for 14 days are usually well tolerated. Procarbazine comes as capsules of 50 mg each.

7.7.3.1 Hematologic

Toxicity (neutropenia, thrombocytopenia) may commence 1 week after the beginning of the treatment, and it can persist up to 2 weeks after withdrawal.

7.7.3.2 Gastrointestinal

Nausea and vomiting can usually be prevented by standard antiemetic treatment.

7.7.3.3 Immunologic and Skin Rash

Hypersensitivity reactions with eosinophilia and fever are common. The reactions can be IgE-mediated but are also associated with a type III reaction manifested by pulmonary toxicity and cutaneous reactions [36]. The higher frequency of hypersensitivity reactions in brain tumor patients has been associated with the concomitant administration of antiepileptic drugs [37]. A diffuse, pruritic, erythematous maculopapular rash has been reported in 12–35% of glioma patients. Note that procarbazine inhibits alcohol dehydrogenase and may cause disulfiram-like reactions when a patient consumes alcohol.

7.7.3.4 Neurologic

Drowsiness and peripheral neuropathy are regularly seen.

7.7.3.5 Respiratory

Rare cases of pneumonitis (see immunologic) have been reported; it may be severe and irreversible. The treatment is procarbazine withdrawal and corticosteroid therapy [38].

7.7.3.6 Hypertensive Crisis

Food containing high levels of tyramine (e.g., red wine, overripe bananas, mature cheese) may cause hypertensive crisis, since procarbazine is a monoamine oxidase (MAO) inhibitor.

7.7.4 Vincristine

Vincristine is a vinca alkaloid that binds to tubulin dimers, inhibiting microtubule assembly and in turn blocking cell division during the mitotic phase [39]. The side effects of vincristine are dependent on the total dose given. The dose-limiting side effect is neurotoxicity. Recent studies have questioned whether vincristine sufficiently penetrates through the blood–brain barrier, and it may not be an effective agent against brain tumors [40]. The standard weekly dose is 1.4 mg/m^2 (usually capped at a maximum dose of 2 mg), as part of the PCV regimen given on days 8 and 29.

The most common side effect is alopecia, while the most troublesome is neuromuscular adverse reactions. Leukopenia and severe myelosuppression are rare. Vincristine is metabolized in the liver via the CYP3A4-mediated enzymes; it may thus increase metabolism of CYP3A4-dependent antiepileptic drugs. Caution is advised in patients with hepatic insufficiency.

7.7.4.1 Alopecia

This is the most common side effect. Regrowth of hair usually happens 6 weeks after the interruption of treatment.

7.7.4.2 Neuromuscular

Frequently, a sequence in the development of the neuromuscular side effects can be observed with the treatment continuation. The initial sensory impairment and

paresthesia are followed by neuropathic pain, and finally motor difficulties occur. No treatment that could reverse the neuromuscular manifestations has so far been reported.

7.7.4.3 Gastrointestinal

Constipation with or without pain has been regularly seen; therefore, prophylactic laxatives should be proposed. Rarely, paralytic ileus can be seen, especially in young and elderly patients, which upon withdrawal of vincristine can regress spontaneously.

7.7.4.4 Ocular

Rarely, visual side effects such as transient cortical blindness, optic nerve atrophy with blindness, and nystagmus can occur.

7.7.4.5 Accidental Extravasation

It can cause severe local reaction and tissue necrosis. Hyaluronidase injection at the site of extravasation must be considered, since vincristine breaks down hyaluronic acid in the connective/soft tissue, allowing the further dispersion of vincristine. Heat packs applied for 20 min QID during 3 days are recommended because this can lead to vasodilatation and consequently to diffusion and elimination of the drug from the site of injection [41].

7.7.5 Bevacizumab (Avastin)

Bevacizumab is a monoclonal neutralizing antibody inhibiting the growth factor VEGF-A, the ligand to the VEGF receptor, highly expressed on tumor-associated endothelial cells [42]. This is an attractive treatment target in patients with glioblastoma because this tumor is highly vascular and expresses high levels of VEGF-A. The commonly used dose of bevacizumab is 10 mg/kg every 2 weeks, although lower doses might be equally effective. Formal dose-finding studies in brain tumors were not conducted. Bevacizumab is approved in recurrent/relapsed glioblastoma in the USA and Switzerland. In many European countries, it is used regularly, although the extension of the indication to brain tumors was rejected by the European Medicines Agency due to the absence of any controlled efficacy data. Definitive phase III trials are finally ongoing.

While bevacizumab clearly allows the reduction of corticosteroid therapy and will lead to temporary neurologic improvement, particularly in patients with severe peritumoral edema, its effect on survival is less evident and contested. The possible modest benefit of bevacizumab has to be balanced against potential risks and toxicity and, ultimately, cost [43], but in any case the benefit that has been documented in PFS and also improved maintenance of baseline quality of life and performance status and neurological functions were observed with bevacizumab in upfront study [44]. This symptomatic effect suggests that bevacizumab remains a useful treatment in CNS tumor given functional consequence of mass effect in the brain.

The most common side effects are hypertension, asthenia, fatigue, vomiting, diarrhea, and abdominal pain, while the most serious side effects are gastrointestinal perforation, hemorrhage, and both arterial and venous thromboembolic events. There is no myelosuppression when used as a single agent.

It should be noted that administration of bevacizumab leads to a reduction in contrast enhancement, the standard metric of objective response, making the radiologic follow-up difficult. Contrast-enhanced magnetic resonance imaging has revealed a significant reduction of the vascular supply, as evidenced by a decrease in intratumoral blood flow and volume. The vascular remodeling induced by anti-VEGF-A treatment leads to a more hypoxic tumor microenvironment. Concerns have been raised that the tumor's remodeling may lead to a more aggressive tumor phenotype. A metabolic change in the tumor cells toward glycolysis leads to enhanced tumor cell invasion of the normal brain tissue [45].

7.7.5.1 Hypertension

Bevacizumab is thought to induce hypertension by decreasing nitric oxide production, resulting in vasoconstriction [46]. This also leads to increased sodium reabsorption in the kidney. Hypertension is a dose-dependent side effect; the frequency increases exponentially with increased doses [47]. With the commonly used high doses of bevacizumab (10 mg/kg), hypertension of any degree has been observed in up to one-third of the patients; however, it was considered severe (≥grade 3, i.e., systolic blood pressure >180 mmHg and diastolic blood pressure >110 mmHg) in only 5% [48]. Preexisting hypertension should be treated before initiation of bevacizumab. Hypertensive exacerbation will further increase the risk for intracranial hemorrhage.

Figure 7.2 shows the management of hypertension and proteinuria. The management of bevacizumab-induced hypertension follows the general principles of hypertension treatment [49]. In patients with cardiovascular risk factors, the treatment goal is 130/80; in others, 140/90. The antiangiogenic treatment should be withdrawn if clinically significant hypertension persists despite proper management or in case of a hypertensive crisis or symptomatic hypertensive encephalopathy (headaches, attention disorder, confusion, coma).

Patients with previous hypertension are, like all hypertensive patients, at higher risk of developing proteinuria. A potential mechanism for proteinuria is by the inhibition of VEGF on the podocytes leading to renal damage [50]. Urinary dipstick analysis should be performed before initiating and during the treatment.

As long as proteinuria over 24 h is not less than 2 g, bevacizumab should not be given. Nephrotic syndrome occurs in 0.5% of patients, and treatment must be withdrawn. Proteinuria is seen less commonly in patients with CNS tumors than in other cancer types, likely explained by the shorter exposure to bevacizumab due to tumor progression occurring at a median of 4 months. Similar to patients with hypertension and proteinuria, agents such as angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs) are the first choice.

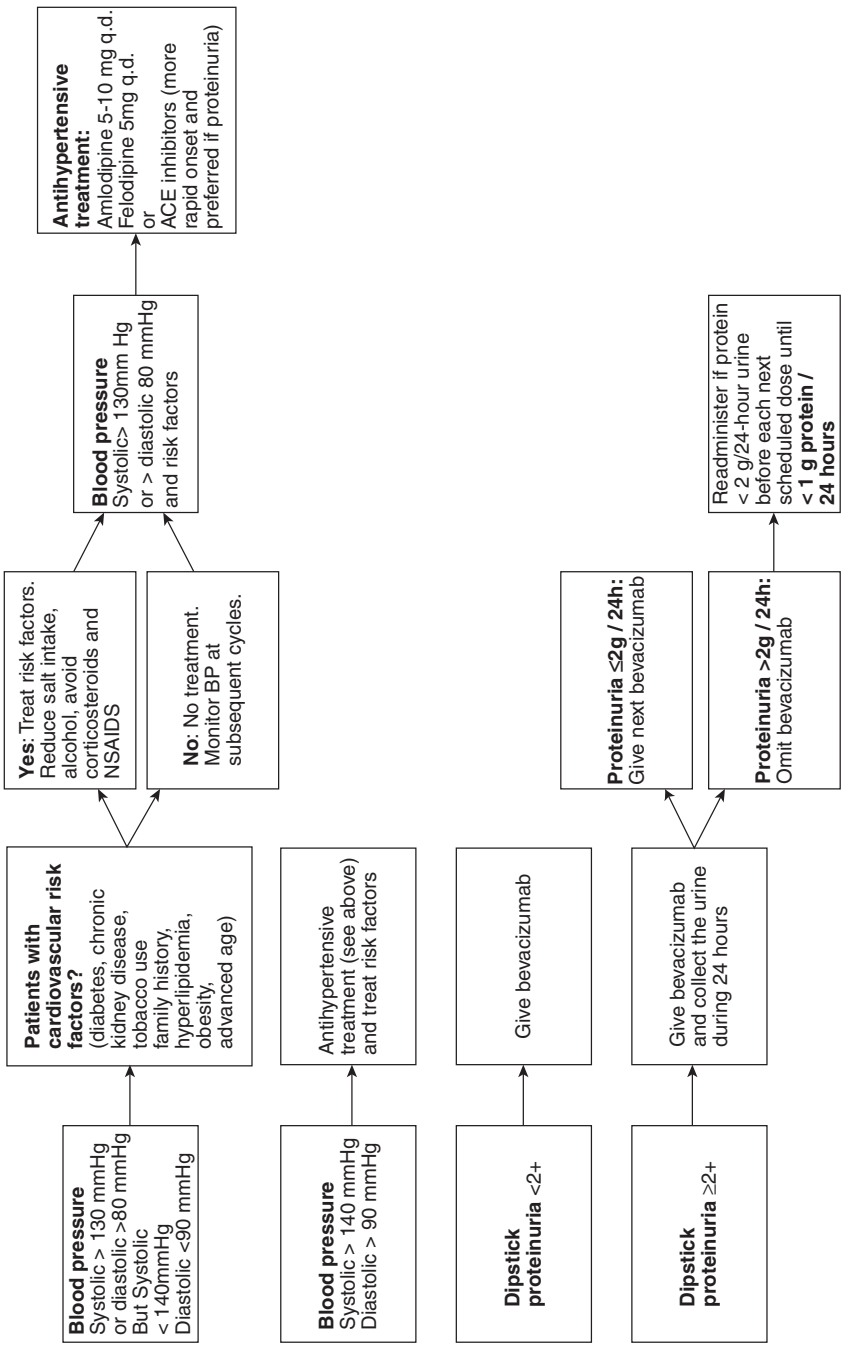

Fig. 7.2 Management of hypertension and proteinuria

7.7.5.2 Arterial and Venous Thromboembolism

Patients with gliomas are at higher risk of venous thrombotic events [51], while the incidence of arterial thromboembolism is not known to be increased. Patients treated with bevacizumab are at higher risk of developing arterial and/or venous thromboembolism [52]. This includes stroke, transient ischemic attacks, myocardial infarction, deep venous thrombosis, and pulmonary embolism. Patients with a previous history of arterial thromboembolism or age older than 65 are at higher risk of developing thromboembolic complications and must be carefully monitored. Bevacizumab therapy should be definitively discontinued in patients having presented with an arterial thrombotic event. The presence of a venous thromboembolic event is a relative contraindication to continuation of bevacizumab therapy; risks and benefits need to be evaluated individually. The requirement of systemic anticoagulation may slightly increase the risk for an intracranial hemorrhage, a risk that is already more pronounced owing to the presence of recurrent tumor in the brain (high vascularization of recurrent glioblastoma may lead to spontaneous bleeding) and further exacerbated by bevacizumab therapy. Nevertheless, current, albeit limited, experience indicates no substantial increase of serious intracranial hemorrhage when patients are treated simultaneously by systemic anticoagulation and bevacizumab [53]. Low-molecular-weight heparins (LMWH) are more often used than oral anticoagulants, since fewer drug interactions are expected with potentially improved efficacy [54].

7.7.5.3 Bleeding

Patients treated with bevacizumab have an increased risk of bleeding, especially at the tumor site [55]. Higher doses of bevacizumab increase the risk of bleeding. The mechanism of the bleeding is thought to be via inhibition of the endothelial cell survival and proliferation leading to damaged blood vessels. The most common type of bleeding is epistaxis, but more serious bleeding like intracerebral, gastrointestinal, or pulmonary can also be seen. If any grade 3 or 4 bleeding occurs, the treatment must be withdrawn. The risk of intracranial hemorrhage does not seem to be more elevated in patients with glioblastoma than in other patients treated with bevacizumab. Intracranial bleeding more frequently occurs during progression, regardless of bevacizumab use.

7.7.6 Surgical Complications After Prior Bevacizumab Therapy

7.7.6.1 Wound Healing

Antiangiogenic therapy interferes with wound healing [56]. Vascular endothelial growth factor is essential for neovascularization, and bevacizumab interferes with this mechanism. The long biological half-life of bevacizumab (median, 20 days; range, 11–50 days) has led to the recommendation not to administer bevacizumab 4 weeks before and 4 weeks after undergoing major surgery or before complete healing of the wound. One study showed that bevacizumab interferes more with wound healing if it is given preoperatively than postoperatively [57].

7.7.6.2 Gastrointestinal Perforation

In a large meta-analysis with 12, 294 patients, perforation was seen in 1% of patients [58]. Most relevant risk factors in brain tumor patients are constipation, diverticular disease, peptic ulcers, and concomitant use of corticosteroids. In any case of gastrointestinal perforation, the treatment must be immediately withdrawn.

7.7.6.3 Heart Failure

In clinical trials, congestive heart failure has been seen in patients receiving bevacizumab. The symptoms are from asymptomatic reduction of left ventricle ejection fraction on cardiac ultrasound to symptomatic heart failure needing inpatient care. Many of these studies included breast cancer patients after prior exposure to anthracyclines and/or trastuzumab. One study suggests that the toxicity may be spontaneously reversible [59].

7.7.6.4 Perfusion Reactions

Patients may develop hypersensitivity and infusion reactions. This is seen in less than 5% of patients. The majority of reactions are mild to moderate. More severe reactions were noted in 0.2% of patients. Premedication is not warranted. If a reaction occurs, the infusion shall be stopped and symptoms treated. Rechallenging patients can be discussed, but it must be based on the goals of the therapy and the severity of the reaction.

7.7.6.5 Posterior Reversible Encephalopathy Syndrome

One of the infrequent but very serious side effects is posterior reversible leukoencephalopathy (PRLE) [60]. The differential diagnosis between PRLE and hypertensive encephalopathy can be difficult. The main symptoms are headache, seizures, altered mental status, nausea, troubled vision, or cortical blindness; most patients are markedly hypertensive. At CT/MR imaging, the brain typically demonstrates focal regions of symmetric hemispheric edema. It is thought that the causes of PRLE can be failure of cerebral vasomotor autoregulation due to hypertension or primary endothelial damage. The mechanisms resemble preeclampsia. The symptoms usually resolve with efficient treatment of hypertension and with withdrawal of bevacizumab.

7.8 Other Commonly Used Agents in CNS Malignancies

For the treatment of germ cell tumors, primitive neuroectodermal tumors (PNET), and medulloblastoma, combination regimens including ifosfamide, cisplatin or carboplatin, and etoposide are frequently administered. The backbone of treatment of primary CNS lymphoma is high-dose methotrexate, either alone or in combination with cytarabine or ifosfamide (±the monoclonal antibody rituximab). We briefly discuss ifosfamide; cytarabine and methotrexate are reviewed in the section on leptomeningeal disease. For the other agents, the reader should refer to other sections of this book.

7.8.1 Ifosfamide

Ifosfamide is a nitrogen mustard alkylating agent and an analogue of cyclophosphamide. First, ifosfamide is activated to 4-hydroxyifosfamide in the liver, which is then transformed into the active compound isoaldophosphamide. In addition to myelosuppression, characteristic toxicities of this agent include hemorrhagic cystitis, renal insufficiency, and ill-defined diffuse cognitive and cerebellar symptoms. Common dosing is 750–1000 mg/m^2/day as a continuous several-hour infusion for 4–5 days. The usual dose for medulloblastoma is 900 mg/m^2/day in a continuous infusion over 5 days [61].

7.8.1.1 Gastrointestinal

Nausea and vomiting is seen in approximately half of patients. Usual antiemetic prophylaxis by 5-HT3 antagonists is recommended.

7.8.1.2 Dermatologic

Reversible alopecia is very common.

7.8.1.3 Neurologic

Ten to twenty percent of patients will have symptoms of encephalopathy such as hallucinations, drowsiness, confusion, and depressive psychosis. Drowsiness is the most common symptom, and it can rapidly progress to coma. These symptoms are seen from a couple of hours to up to a couple of days after the administration of the drug. In any case, the drug should be immediately suspended. After halting the administration, the median duration of the symptoms is 3 days. Interactions with other CNS-depressing drugs must be considered and the drugs withdrawn. High doses of ifosfamide illogical truncation administered over a short time, preexisting neurologic or renal dysfunction, and low serum albumin appear to be significant risk factors. In patients with grade 3–4 encephalopathy, IV administration of methylene blue (50 mg every 4 h until symptoms resolve) may be considered. The pathophysiology of this encephalopathy is poorly understood, but the cause seems to be due to chloroacetaldehyde accumulation in the nervous system. It can be (1) directly neurotoxic, (2) deplete CNS glutathione, and (3) inhibit mitochondrial oxidative phosphorylation, leading to impaired fatty acid metabolism. Methylene blue has a redox potential and restores mitochondrial respiratory chain function; it prevents transformation of chloroethylamine into chloroacetaldehyde and restores hepatic gluconeogenesis [62]. Little evidence exists for the prophylactic use of methylene blue in combination with ifosfamide.

7.8.1.4 Kidneys and Bladder

Micro- or macrohematuria is seen very commonly. It is dose dependent and can be prevented and/or alleviated by simultaneous administration of mesna. Mesna is an organosulfur compound. It is converted to an inactivated form in the blood and filtered by the kidneys, where it is reactivated. Ifosfamide and cyclophosphamide, when given in high doses, produce the metabolite acrolein, which is toxic to the

bladder. Mesna binds to and inactivates acrolein, consequently reducing local side effects in bladder. If cystitis develops during ifosfamide administration despite correct mesna dosing, the treatment should be suspended until micro- or macrohematuria disappears. During ifosfamide infusion correct hydration is important, and the bladder must be emptied on a regular basis. Tubular damage has been proposed to be the cause of renal failure seen in some patients. Mesna does not protect against renal toxicity.

7.8.1.5 Hematologic

Patients pretreated with other chemotherapy regimens or radiotherapy and with preexisting renal insufficiency are at increased risk of myelotoxicity, which can sometimes be very important. Leukopenia is seen more often than thrombocytopenia. The nadir is at 8–10 days and is usually normalized at 3–4 weeks.

7.9 Promising New Approach and Targeted Therapies: Checkpoint Inhibitors

A promising avenue of clinical research in brain cancer is the use of immune checkpoint inhibitors. These treatments work by targeting molecules that serve as checks and balances on immune responses. By blocking these inhibitory molecules, these treatments are designed to unleash or enhance pre-existing anticancer immune responses. The following molecules are currently recruited: nivolumab (Opdivo®), durvalumab (MEDI4736), ipilimumab (YERVOY®), and pembrolizumab (KEYTRUDA®). The most important treatment-related adverse events associated with immune checkpoint inhibitor are autoimmune effects. Immune toxicities of all bodies have previously been reported in pivotal studies of other tumor location (melanoma, lung cancer, etc.). Systemic toxicity will need to be closely monitored and includes colitis, endocrinopathies, and dermatologic manifestation; peripheral nervous system toxicities such as Guillain–Barré syndrome and myasthenia gravis have been reported. CNS toxicities, including transverse myelitis and inflammation of brain parenchyma (in the absence of brain metastasis), have also been reported with checkpoint inhibitors. The key challenge of checkpoint inhibitor development in CNS will be to balance treatment efficacy and immune neurological toxicity. To date, no studies have been published to assess that specific field.

At the annual meeting of the American Society of Clinical Oncology, held June 2016, in Chicago, phase 1 data from the CheckMate 143 trial was presented. The trial was designed to evaluate the safety and tolerability of nivolumab, alone or in combination with ipilimumab, in patients with recurrent/progressive glioblastoma (phase I). The 12-month overall survival (OS) rate was 40% with nivolumab monotherapy. Median OS was 10.5 months. Discontinuation due to adverse events was reported in four patients treated with ipilimumab associated with nivolumab cohort. No discontinuation was reported with nivolumab alone. The study found no grade 5 treatment-related adverse events. Nivolumab alone did not cause any grade 3 or 4 adverse events. A 90% rate of grade 3–4 were reported in the cohort of patients

treated with nivo 1 mg/kg + ipi 3 mg/kg every 3 weeks and 25% in the cohort nivo 3 mg/kg + ipi 1 mg/kg Q3W. These adverse events included diabetic ketoacidosis, hypocalcemia, hypomagnesemia, hyperthyroidism, colitis, diarrhea, cholecystitis, sepsis, muscular weakness, malignant neoplasm progression, being in a confused state, acute kidney injury, hypotension, and increased alanine aminotransferase, aspartate aminotransferase, amylase, and lipase. Meningo-(radiculitis), polyradiculitis, cardiac arrhythmia, asystolia, and paresis were reported [63].

Pembrolizumab had a 6-month progression-free survival (PFS) rate of 44% and a manageable safety profile for patients with recurrent PD-L1-positive glioblastoma multiforme, according to findings from the phase Ib KEYNOTE-028 trial presented at the 2016 Society for Neuro-Oncology Annual Meeting. Median PFS was 3 months and the 12-month PFS rate was 16%. The median overall survival (OS) was 14 months. Overall, 15% of patients experienced grade 3/4 adverse events (AE). Less than 10% of the patients experienced immune-related AEs, which included colitis in two patients (8%), hypothyroidism in two (8%), hyperthyroidism in two (8%), and drug eruption in one (4%). The median follow-up was 60.9 weeks. No grade 4 cerebral edema occurred. No treatment-related deaths or discontinuations occurred [64].

7.10 Tumor-Treating Fields: A Novel Treatment Modality

Tumor-treating fields (TTFields) are an antimitotic treatment that selectively disrupts the division of cells by delivering low-intensity, intermediate-frequency (200 kHz) alternating electric fields via transducer arrays applied to the shaved scalp. In preclinical models, TTFields have been shown to cause mitotic arrest and apoptosis by disrupting mitotic spindle formation during metaphase and causing dielectrophoretic movement of polar molecules during cytokinesis. TTFields is a novel noninvasive therapeutic option for recurrent GBM [65]. It has been evaluated in randomized phase 3 trials in glioblastoma (GBM) and demonstrated to prolong progression-free survival (PFS) and overall survival (OS) when administered together with standard maintenance temozolomide (TMZ) chemotherapy in patients with newly diagnosed GBM. Median OS from randomization (ITT) was 19.6 months (95% CI, 16.6–24.4 mo) in the TTFields plus TMZ group compared with 16.6 months (95% CI, 13.6–19.2 mo) in the TMZ control group (HR: 0.74 [95% CI, 0.56–0.98]; $P = 0.03$). Toxicity related to TTFields therapy consisted, by the nature of this treatment, mainly of local skin irritation. This is usually mild, self-limiting, easily manageable with local application of steroid-containing ointments and may require an occasional treatment break for a few days. Some mild-moderate (grade 1–2) skin reaction is observed in up to half of patients. Severe (grade 3) reactions were again seen in only 2% of patients. Allergic contact dermatitis, irritant contact dermatitis, folliculitis, and erosion are reported. When compared with TMZ maintenance treatment alone, the addition of TTField did not result in any modification of the side effects in patients with newly diagnosed GBM.

7.11 Inhibitors of FGFRs

A small subset of GBMs and *IDH* wild-type gliomas (around 3%) harbors oncogenic chromosomal translocations that fuse in-frame the tyrosine kinase coding domains of fibroblast growth factor receptor (*FGFR*) genes (*FGFR1* or *FGFR3*) to the transforming acidic coiled-coil (*TACC*) coding domains of *TACC1* or *TACC3*, respectively [66]. The *FGFR-TACC* fusion protein displays oncogenic activity in vitro and in vivo and appears as a novel promising activable target. The FGFR family consists of four members each composed of an extracellular ligand-binding domain, a transmembrane domain, and an intracellular cytoplasmic protein tyrosine kinase domain. Receptor activation leads to the recruitment and activation of specific downstream signaling partners that participate in the regulation of diverse process such as cell growth, cell metabolism, and cell survival. In addition hotspot activating mutations on *FGFR1* have been reported in specific subgroups such as pilocytic astrocytoma in adults and midline diffuse gliomas.

Inhibition of FGFR oncogenic drivers may then represent a novel approach by competitive and covalent inhibitors. A phase Ib/phase II clinical trial testing efficacy and tolerability of an of AZD4547 in glioma patients harboring *FGFR-TACC* fusions at recurrence is actually ongoing and test the efficacy of this selective inhibitor of FGFR-1, 2, and 3 receptor tyrosine kinases in this selected subgroup of patients (NCT02824133).

Common toxicities of anti-FGFR therapies include fatigue, constipation, mucositis, skin and eye toxicity, hyperphosphatemia, and cardiac dysfunction.

7.12 BRAF Inhibitors

The *B-Raf* proto-oncogene serine/threonine kinase (B-Raf) is a member of the Raf kinase family. The *BRAF* V600E mutation occurs frequently in certain brain tumors, such as pleomorphic xanthoastrocytoma, ganglioglioma, and pilocytic astrocytoma, and less frequently in epithelioid and giant cell glioblastoma. Therapeutic opportunity is presented by the finding that BRAF V600E is highly druggable. *BRAF* V600E inhibitors reduce phosphorylation of mitogen-activated protein kinase (MAPK) with subsequent downstream effects on apoptosis and cell cycle inhibition. The most common AEs of all severity grades of BRAF inhibitors were rash, arthralgia, fatigue, photosensitivity, alopecia, and nausea. Phase II trials are actually ongoing to test efficacy and tolerance (NCT01748149).

7.13 Crizotinib

Crizotinib (PF-02341066) is an ATP-competitive, small-molecule inhibitor of the receptor tyrosine kinases (RTKs*) c-Met* (also known as hepatocyte growth factor receptor) and anaplastic lymphoma kinase (ALK), for the potential treatment of cancers dependent on these oncogenic kinases for growth and survival. The drug is

associated with cardiac adverse events. *MET* amplifications have been documented in around 5% of glioblastoma, and preliminary experiences suggest a signal of activity in recurrent GBM patients harboring *MET* amplifications. Phase II trials are actually ongoing to test efficacy and tolerance (NCT02034981).

7.14 Metastasis of CNS Tumors

Brain metastasis is increasingly common, affecting 20–40% of cancer patients. After diagnosis, survival is usually limited to months in these patients. Brain metastases arise from hematogenous spread of several tumors: lung, breast, prostate, ovarian, and esophageal cancer and melanoma. Usually they follow the course of the bloodstream, so the distribution is supratentorial (85%) and posterior fossa (15%). Slowly progressive focal neurological signs of intracranial hypertension and epilepsy can be observed. Diagnosis is made by neuroimaging. The number of metastases dictates the therapeutic approach, although it is still debated if surgical resection and radiotherapy can accomplish some degree of amelioration of OS. Treatment for brain metastasis includes whole brain radiation therapy, surgical resection, or both. These treatments aim to slow progression of disease and to improve or maintain neurologic function and quality of life. Radiosurgery it's possible but lesion's diameter does not exceed 3–3.5 cm. Radiosurgery offers the potential of treating patients with surgically inaccessible metastases. Still controversial is the need for WBRT after surgery or radiosurgery: local control seems better with the combined approach, but overall survival does not improve. Late neurotoxicity in long-surviving patients after WBRT is not negligible; to avoid this complication, patients with favorable prognostic factors must be treated with conventional schedules of RT, and monitoring of cognitive functions is important. WBRT alone is the treatment of choice in patients with single brain metastasis not amenable to surgery or radiosurgery, and with an active systemic disease, and in patients with multiple brain metastases. A small subgroup of these latter may benefit from surgery. The response rate of brain metastases to chemotherapy is similar to the response rate of the primary tumor and extracranial metastases, some tumor types being more chemosensitive (small cell lung carcinoma, breast carcinoma, germ cell tumor).

7.15 Treatment of Leptomeningeal Carcinomatosis (Carcinomatous Meningitis)

Meningeal carcinomatosis, present in 25% of brain tumors, is the presence of cancer cell in CSF as isolated colonies. Melanoma, breast and lung cancer, and hematologic and lymphoid malignancies are the most common origins of leptomeningeal dissemination [67]. Localized metastases may be treated by focal irradiation, while diffuse meningeal involvement requires intrathecal or high-dose systemic chemotherapy. Efficacy of intrathecal therapy may be limited by perturbed cerebrospinal fluid flow. Occasionally, direct intraventricular injection or access over a surgically

implanted reservoir (Ommaya or Rickham) is preferred over administration by lumbar puncture, thus allowing a more homogenous distribution of the chemotherapeutic agent. The objective is to relieve and control symptoms, while often additional systemic therapy for adequate antitumor control is needed. In patients with high-risk hematologic malignancies, prophylactic intrathecal chemotherapy is often recommended [68]. Nevertheless, literature on the value of intrathecal therapy remains scarce and lacks controlled trials.

Three agents are used for intrathecal chemotherapy: cytarabine, methotrexate, and thiotepa. Adverse reactions are not uncommon. When administered intrathecally, chemical aseptic meningitis is the most common side effect seen in 20–40% of patients and is characterized by fever, nausea and vomiting, headache, back pain radiating to the extremities, and photophobia. This can be reduced by using preservative-free diluent (saline) and preservative-free chemotherapy preparations. Late adverse events occurring more than 4–6 months after treatment, such as leukoencephalopathy with symptoms such as dementia and ataxia, must not be forgotten. The incidence is probably underestimated; it is probably higher than 20% in patients surviving more than 4 months.

7.15.1 Cytarabine

Cytarabine (araC) is an antimetabolic agent that damages DNA formation during the S phase of the cell cycle. The liposomal formulation of cytarabine [69] is lipophilic and has a long half-life. Liposomal cytarabine (DepoCyte) is lipophilic long half-life. The liposomal formula maintains a therapeutic concentration in the CSF for 28 days, while the conventional form is entirely eliminated within 1–2 days. Conventional intrathecal dose is 50 mg; with a short half-life, this should be repeated two times a week. In contrast, a liposomal formulation of cytarabine for prolonged cytotoxic exposure exists, thus requiring one administration (50 mg) every 2 weeks only. Liposomal cytarabine is approved for leptomeningeal metastases of hematologic malignancies.

7.15.1.1 Systemic Doses of Cytarabine

Cytarabine is the most frequently used agent against acute leukemia. For more detailed information, the reader is referred to the chapter on hematologic malignancies.

7.15.1.2 Neurologic

In approximately 10% of patients treated with high doses ($\geq$3 g/m^2) administered intravenously every 12 h, an acute cerebellar syndrome develops [70, 71]. The initial symptom is somnolence. Cerebellar signs are then noted on neurologic examination, and patients may not be able to ambulate. In many patients the symptoms usually resolve after the withdrawal of cytarabine, although prolonged and persistent symptoms have been observed. There is no specific therapy other than suspending chemotherapy.

7.15.1.3 Hematologic

High doses of cytarabine will induce profound myelosuppression.

7.15.1.4 Gastrointestinal

Diarrhea, mucositis, intestinal ulceration, and ileus can be seen. The gastrointestinal side effects are often dose limiting.

7.15.2 Methotrexate

Methotrexate (MTX) is a folate antimetabolite, thus interfering with DNA synthesis, repair, and cellular replication. Methotrexate has been used for a wide variety of cancers (sarcomas, lymphomas, breast cancer) and also for autoimmune disorders. Methotrexate has a very good distribution in all tissues [72]. While passage through the blood–brain barrier requires administration of high systemic doses to obtain adequate drug concentrations in the central nervous system, intrathecal administration will allow the use of lower doses for the control of leptomeningeal disease with less systemic toxicity. However, drug penetration is limited to the distribution of the cerebrospinal fluid. The dose of MTX varies greatly from oral weekly 10 mg/m^2 for rheumatoid arthritis to high-dose chemotherapy of $\geq$3 g/m^2 in primary brain lymphomas or up to 12 g/m^2 for osteosarcoma patients [73]. The commonly used dose for intrathecal administration is 12.5–15 mg/dose, which is to be repeated once or twice per week until the CSF clears and then once a week or once a month for maintenance treatment. A more intensive regimen proposed is 15 mg/day for 5 consecutive days every 2 weeks [74]; its relative efficacy has not been formally investigated.

7.15.2.1 Hematologic

Myelosuppression can be seen when administered intrathecally.

7.15.2.2 Transverse Myelopathy

An isolated spinal cord dysfunction develops rarely hours to days after the administration of MTX without compressive lesion. Patients develop back or leg pain followed by paraplegia, sensory loss, and sphincter dysfunction. The majority of patients recover, but further administration is contraindicated.

7.15.2.3 Acute Encephalopathy

Somnolence, confusion, and seizures are seen within 24 h after treatment; they usually resolve spontaneously.

7.15.2.4 Subacute Encephalopathy

After repeated injections of MTX, motor function impairments such as paraparesis/paraplegia, tetraplegia, cerebellar dysfunction, cranial nerve paralysis, and seizures can occur.

7.15.2.5 Methotrexate Administered in High Doses Intravenously

Intravenous administration of high doses (>3 g/m^2) of MTX may also be used in the treatment of meningeal disease to achieve cytotoxic doses in the CNS. The incidence and severity of acute side effects are related to dose and frequency of administration. In primary lymphoma of the central nervous system, high-dose IV MTX is the backbone of therapy. Methotrexate is also an active agent in systemic breast cancer and may allow the control of leptomeningeal disease.

Younger patients seem to better tolerate the high-dose MTX therapy, presumably due to better end-organ function and rapid elimination. Caution is to be used in patients with renal and hepatic insufficiency. The common side effects of high-dose MTX are alopecia, neutropenia, renal toxicity (more commonly in older patients), nausea, diarrhea, and stomatitis. Hepatic toxicity with transaminitis is seen.

The presence of third-space fluids is a contraindication to the administration of high-dose MTX. High concentrations of MTX can accumulate in these spaces, leading to a prolonged MTX exposure and increased toxicity. Drainage of ascites or pleural effusion must be done before introducing the drug.

The use of high-dose IV MTX has been associated with the development of chronic delayed leukoencephalopathy in patients with or without a history of craniospinal irradiation.

High-dose MTX is a potential lethal dose, and before leucovorin rescue was initiated as a standard part of the regimen, 6% drug-related death was noted, most frequently due to the immunosuppression. Therefore, high-dose MTX administration is followed by leucovorin rescue to inhibit the toxicity of MTX on the normal cells (Fig. 7.3). The timing of the rescue is important, since introducing too early the rescue leads to a diminished effect on the tumor cells. The administration of leucovorin can be delayed up to 24–36 h without, in general, important MTX toxicity. Several schedules of leucovorin rescue exist. If the concentration of MTX is higher than 1 μmol/L at 48 h, increasing the dose of leucovorin must be considered. The rescue must continue for at least 72 h and until the concentration of MTX is at a nontoxic level (0.01–0.1 μmol/L).

Methotrexate is principally excreted by the kidneys. A glomerular filtration rate of 60 mL/min is in general considered as a minimum for high-dose MTX administration. It should be noted that the presence of a normal serum creatinine does not predict MTX toxicity [72]. A high urine flow and an alkaline pH must be ensured to prevent precipitation of MTX in the urine, causing nephrotoxicity.

7.15.3 Thiotepa

Thiotepa is an alkylating agent. It crosses the blood–brain barrier well, achieving high concentrations and resulting in high levels of the active metabolite, TEPA. When administered intrathecally, thiotepa is cleared from CSF within minutes and completely eliminated within 4 h. The initial dose is 10 mg twice weekly for 4 weeks followed by one injection per week for another 4 weeks, with maintenance with one

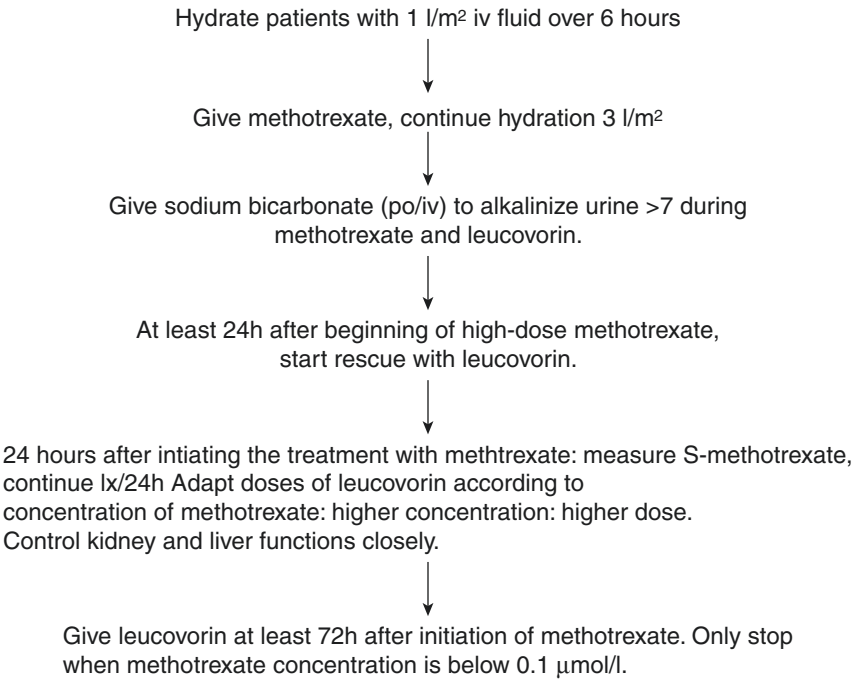

Fig. 7.3 Administration of high-dose methotrexate with leucovorin rescue

injection per month. Due to its important hematotoxicity, intrathecal administration is preferred, because it is generally well tolerated.

7.15.3.1 Hematologic

Systemic myelosuppression has been seen even with intrathecal administration. Systemic administration of thiotepa causes profound bone marrow suppression, especially thrombocytopenia.

7.16 Symptomatic and Supportive Care

Symptom management—seizures, cerebral edema (swelling in the brain around the tumor), and obstructive hydrocephalus (increased pressure within the brain due to blockage of the flow of cerebrospinal fluid within the brain)—can all result in serious symptoms. Each of these requires a different therapeutic approach.

The same medications used to treat epilepsy are usually successful in controlling seizures associated with brain tumors. However, seizures may be more difficult to control in people with brain tumors, particularly low-grade gliomas. If medications are not effective, surgery to remove part of the tumor may be recommended in an attempt to reduce seizure activity. The most common side effects of antiepileptic

drugs (AEDs) are gastrointestinal toxicity in the form of nausea, vomiting, and diarrhea and skin rash. Further common side effects of AEDs are sleepiness and unsteadiness. Carbamazepine, phenobarbital, phenytoin, and sodium valproate could induce osteoporosis or osteomalacia. Furthermore, AEDs can influence memory, especially when high doses are applied. In case side effects are detected, either dose reduction should be tried or a rotation should be proposed with an AED with a different class of effect. Antiepileptic drugs such as phenytoin, phenobarbital, and carbamazepine induce the hepatic enzyme P450 (enzyme-inducing antiepileptic drugs, EIADs). Several chemotherapeutic agents, including, irinotecan, lomustine, vincristine, and procarbazine, are metabolized by the cytochrome P450. While patients with malignant gliomas are treated with these therapies, their metabolism can be increased and thus can lead to diminished efficacy. Brain tumor patients treated with EIAEDs are recommended to change to third-generation antiepileptic drugs like levetiracetam.

Cerebral edema usually can be treated successfully with steroids; the most commonly used steroid is dexamethasone [75]. Dexamethasone use can be temporary if specific treatment of the tumor is planned, and the treatment is expected to decrease edema. Dexamethasone may be used for a more prolonged period of time if treatment is not currently planned. Dexamethasone may be particularly useful in the late phases of the illness, such as if the tumor recurs and there is no other way to control cerebral edema. One of the problems with long-term use of dexamethasone (particularly high doses) is the potential for side effects (e.g., ulcers, bleeding from the gastrointestinal tract, behavioral changes, thinning of the skin, loss of bone strength, high blood sugar). Thus, the dose of dexamethasone is tapered to achieve the lowest dose that effectively controls symptoms, yet minimize long-term complications. The initial dose of dexamethasone is a 10-mg IV bolus followed by 4 mg every 6 h (16 mg/day). Since this scheme does not follow the normal diurnal changes of blood corticoids, we prefer the scheme of 8 mg twice a day in the morning and at noon. This administration reduces insomnia induced by dexamethasone. In dose-finding studies dexamethasone had been increased up to 40 mg, but there was no evidence for improved effectiveness. Once the desired acute effect has been achieved, the dose of dexamethasone should be rapidly tapered in order to avoid long-term perturbation of the hypothalamic-pituitary-adrenocortical (HPA) axis and toxicity from prolonged corticosteroid administration. Tapering consists in empiric reduction of 2–4 mg every 2–3 days. While the initial reduction in doses—empiric reduction of 2–4 mg every 2–3 days—can be rapid, the final tapering before definitive cessation of the treatment should be done more slowly, with decrements of 0.5–1 mg every 3–7 days, depending on the duration of prior steroid exposure. Common side effects are hyperglycemia, gastritis, gastrointestinal bleeding, osteoporosis, immunosuppression, skin fragility and striae, obesity, psychosis and euphoria, or myopathy with weakness of the lower extremities and neck. Steroid-induced myopathy and secondary diabetes may be misleading of disease progression and need to be excluded. Restrictive steroid prescription and appropriate surveillance may prevent these frequent complications.

Obstructive hydrocephalus may require surgery to bypass the blockage and lower the pressure within the brain.

Conclusions

Malignant gliomas are the most common malignant primary brain tumors and one of the most challenging forms of cancers to treat. Despite advances in conventional treatment, the outcome for patients remains almost universally fatal. This poor prognosis is due to therapeutic resistance and tumor recurrence after surgical removal. Progresses in understanding the molecular pathology of gliomagenesis and oncogenic drivers will open opportunities to rationally develop molecular targeted therapy holding the promise of transforming the care of malignant glioma patients.

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Myeloid Malignancies

8

Laurent Plawny

Abstract

Myeloid malignancies comprise the various myeloid proliferative stem cell disorders. In this chapter, the side effects of the currently used drugs are given as used in the general hematologic clinic. For the various disorders covered, the side effects of the medications are pleomorphic; therefore, for the tyrosine kinase inhibitors in chronic myeloid leukemia, a tabulated summary is given. Hematopoietic stem cells, autologous as well as allogeneic, are not covered. These treatment modalities are used in very specialized units, and the patient's follow-up during the first few months is also done through these units, which are very familiar with the therapies.

Keywords

Myelodysplastic syndromes · Acute myeloid leukemia · Polycythemia vera · Essential thrombocythemia · Chronic myeloid leukemia

8.1 Myelodysplastic Syndrome

8.1.1 5-Azacytidine

5-Azacytidine [1–6] is a hypomethylating agent that has been approved in the treatment of myelodysplasia with low-intermediate and high-intermediate International Prognostic Scoring System (IPSS) in the United States. In the European Union, 5-azacytidine has been approved for myelodysplasia with high IPSS only. Some

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M. A. Dicato, E. Van Cutsem (eds.), *Side Effects of Medical Cancer Therapy*,
https://doi.org/10.1007/978-3-319-70253-7_8

data about its efficacy in chronic myelomonocytic leukemia or in acute myeloid leukemia with low blast count have also been noted.

The side effects of 5-azacytidine are listed below. Hematologic toxicity that results mainly in anemia or thrombocytopenia is observed in most patients. Leukopenia or grade III neutropenia occurs in about one patient out of five and may lead to febrile neutropenia or opportunistic infections. Invasive fungal infections remain an issue in patients receiving 5-azacytidine treatment; therefore, prophylactic antifungal treatment with activity against aspergillus should be discussed in selected patients.

Agranulocytosis or irreversible aplasia is exceptional but is a cause of infectious mortality.

Fever may occur at the time of injection but is mostly related to infection. Nausea and vomiting occur frequently but may be reduced with adequate antiemetic medication.

A recurring problem in patients receiving subcutaneous 5-azacytidine is skin reaction at the infusion site. These reactions can vary from rash to pruritic plaques. Most skin rashes disappear with topical antihistamines or anti-inflammatory creams. The injection technique, however, influences the prevalence of skin lesions. Correct injection that avoids skin contact with the product lowers the occurrence of rash and pruritic plaques by more than a half.

The following are side effects of 5-azacytidine treatment:

8.1.1.1 Hematologic

- Very frequent (>50% of patients): anemia, thrombocytopenia
- Frequent (>20% of patients): leukopenia, neutropenia
- Rare (5–10% of patients): lymphadenopathies, hematomas
- Very rare (<5% of patients): agranulocytosis, aplasia, splenomegaly

8.1.1.2 General

- Very frequent (>50% of patients): fever
- Frequent (>20% of patients): fatigue, anorexia, injection site pain
- Occasional (>10% of patients): epistaxis, febrile neutropenia, weight loss, sweating
- Rare (5–10% of patients): herpes simplex, hypotension
- Very rare (<5% of patients): anaphylactic shock, opportunistic infections (blastomycosis, toxoplasmosis), dehydration, systemic inflammatory response

8.1.1.3 Gastrointestinal

- Very frequent (>50% of patients): nausea, vomiting
- Frequent (>20% of patients): diarrhea, constipation, pharyngitis
- Occasional (>10% of patients): abdominal pain and tenderness
- Rare (5–10% of patients): stomatitis, oral petechiae, mouth hemorrhage
- Very rare (<5% of patients): gastrointestinal hemorrhage

8.1.1.4 Renal

- Rare (5–10% of patients): dysuria, urinary tract infections
- Very rare (<5% of patients): renal failure, hematuria

8.1.1.5 Pulmonary
- Frequent (>20% of patients): cough, dyspnea
- Occasional (>10% of patients): chest pain, upper respiratory tract infection, pneumonia, rhinorrhea
- Rare (5–10 % of patients): wheezing, pleural effusion

8.1.1.6 Cardiac
- Rare (5–10% of patients): tachycardia

8.1.1.7 Cutaneous
- Frequent (>20% of patients): injection site erythema, ecchymosis, petechiae
- Occasional (>10% of patients): pallor, generalized rash, injection site bruising
- Rare (5–10% of patients): cellulitis, injection site pruritus, injection site swelling, dry skin, skin nodules

8.1.1.8 Nervous System
- Frequent (>20% of patients): headache
- Occasional (>10% of patients): anxiety, depression, insomnia
- Rare (5–10% of patients): hypoesthesia
- Very rare (<5% of patients): confusion, convulsions, intracranial hemorrhage

8.1.1.9 Metabolic
- Occasional (>10% of patients): hypokalemia

8.1.1.10 Locomotor
- Frequent (>20% of patients): rigors, arthralgia, pain in limb, back pain
- Occasional (>10% of patients): peripheral edema, myalgia

Teratogenic activity is proven in the animal model. An effective contraceptive method is recommended in patients undergoing 5-azacytidine treatment.

8.1.2 Decitabine

The use of decitabine [1, 2, 7], an intravenous hypomethylating agent, is currently restricted to the United States. It is indicated in myelodysplasia, with low-intermediate or high-intermediate IPSS.

The most common side effects are hematologic, with anemia, thrombocytopenia, and neutropenia occurring in more than 50% of the patients. Febrile neutropenia occurs in about 20% of patients. Opportunistic infections are rare occurrences. Fungal infections like invasive candidiasis have been described in more than 10% of patients. The issue of antifungal prophylaxis in patients receiving decitabine treatment remains an open question.

Metabolic side effects are rather common and consist mainly of hypoalbuminemia and hyperglycemia and elevation of liver enzymes. Close monitoring of glucose levels is therefore recommended.

The side effects encountered in patients receiving decitabine treatment are as follows:

8.1.2.1 Hematologic

- Very frequent (>50% of patients): neutropenia, thrombocytopenia, anemia
- Occasional (>10% of patients): lymphadenopathy
- Rare (5–10% of patients): thrombocythemia
- Very rare (<5%): bone marrow suppression, splenomegaly

8.1.2.2 General

- Very frequent (>50% of patients): pyrexia
- Frequent (>20% of patients): febrile neutropenia, peripheral edema
- Occasional (>10% of patients): rigors, pain, lethargy, dehydration, anorexia
- Rare (5–10% of patients): chest discomfort, catheter site erythema, catheter site pain, injection site swelling

8.1.2.3 Gastrointestinal

- Frequent (>20% of patients): nausea, vomiting, constipation, diarrhea
- Occasional (>10% of patients): abdominal pain, oral mucosal petechiae, stomatitis, dyspepsia, ascites
- Rare (5–10% of patients): gingival bleedings, hemorrhoids, loose stool, tongue ulceration, dysphagia, lip ulceration, abdominal distension, abdominal pain, gastroesophageal reflux, glossodynia
- Very rare (<5%): cholecystitis

8.1.2.4 Renal

- Rare (5–10% of patients): dysuria, urinary frequency

8.1.2.5 Pulmonary

- Frequent (>20% of patients): cough
- Occasional (>10% of patients): pharyngitis, respiratory crackles, hypoxia
- Rare (5–10% of patients): postnasal drip

8.1.2.6 Cardiac

- Rare (5–10% of patients): pulmonary edema
- Very rare (<5% of patients): myocardial infarction, atrial fibrillation

8.1.2.7 Cutaneous

- Frequent (>20% of patients): ecchymosis, petechiae, pallor
- Occasional (>10% of patients): rash, skin lesions, pruritus, alopecia
- Rare (5–10% of patients): urticaria, swelling face

8.1.2.8 Nervous System

- Frequent (>20% of patients): headache

- Occasional (>10% of patients): dizziness, hypoesthesia, insomnia, confusion, anxiety
- Rare (5–10% of patients): blurred vision

8.1.2.9 Metabolic

- Frequent (>20% of patients): hyperglycemia, hypoalbuminemia
- Occasional (>10% of patients): hyperbilirubinemia, hypomagnesemia, hyponatremia
- Rare (5–10% of patients): hyperkalemia

8.1.2.10 Locomotor

- Frequent (>20% of patients): arthralgia
- Occasional (>10% of patients): limb pain, back pain
- Rare (5–10% of patients): chest wall pain, myalgia

8.1.2.11 Infectious

- Frequent (>20% of patients): pneumonia
- Occasional (>10% of patients): cellulitis, candidal infection
- Rare (5–10% of patients): catheter-related infections, urinary tract infection, sinusitis, bacteremia
- Very rare (<5% of patients): Mycobacterium avium infection

Effective contraceptive methods are recommended for men and women during and for a minimum of 12 months following therapy.

8.2 Acute Myeloid Leukemia

8.2.1 Cytarabine

Cytarabine [1, 2, 8–10], an intravenous antimetabolite cytidine analogue, has been widely used as monotherapy or in combination with other agents on the induction of treatment for acute myeloid leukemia. It also has proven efficacy in the treatment of lymphomas, especially mantle cell lymphomas, in which cytarabine-containing regimens have allowed longer progression-free survivals and higher remission rates. Cytarabine is also used in some ALL regimens, mainly in the consolidation phase.

The most common adverse effects are hematologic. Hematologic toxicity occurs regularly in patients receiving cytarabine and consists of deep bone marrow depression. Leukopenia typically follows a biphasic curve, with a first nadir at 7–9 days and a second more profound nadir at days 15–24. Frequent bleeds have been described as a result of thrombocytopenia.

About 10% of patients may experience cytarabine syndrome, which consists of fever, myalgia, chest pain, maculopapular rash, conjunctivitis, and malaise. Cytarabine syndrome can evolve to severe hypotension and requires corticosteroid

treatment. Discontinuation of the treatment must be discussed according to the severity of symptoms.

Nausea and vomiting frequently occur and require prophylaxis with antiemetic treatments. In patients receiving high doses of cytarabine (more than 10 g/week), gastroenterologic side effects can be more marked and include diarrhea and severe colitis, ranging from neutropenic colitis to gastrointestinal bleeding. Rare cases of pancreatitis have been described with experimental doses of cytarabine.

Febrile neutropenia is a common finding in patients receiving cytarabine-based regimens. If bacterial causes are the most frequent, invasive fungal infections are a frequent occurrence, especially in AML patients. In selected patients, antifungal prophylaxis active against aspergillosis must be considered.

Central nervous system toxicity occurs mostly in elderly patients receiving high-dose regimens. Cerebellar toxicity is the main feature in patients; it results in ataxia and slurred speech. Infrequently, patients can experience confusion or fatal encephalitis. The use of prophylactic pyridoxine treatment has been debated. Conjunctivitis is also a frequent finding in patients. Prophylactic topical corticosteroids may be useful in patients receiving high-dose cytarabine.

The following toxicities have been described with cytarabine:

8.2.1.1 Hematologic

- Bone marrow depression: anemia, leukopenia, thrombocytopenia
- Thrombophlebitis (frequent)

8.2.1.2 General

- Cytarabine syndrome.
- Severe sepsis may occur from leukopenia.
- Rare: allergic reaction, anaphylactic shock.

8.2.1.3 Gastrointestinal

- Frequent: anorexia, nausea, vomiting, diarrhea, oral and anal mucositis, hepatic dysfunction
- Rare: esophageal ulceration, bowel necrosis, pancreatitis

8.2.1.4 Renal

- Rare: renal dysfunction, urinary retention

8.2.1.5 Pulmonary

- Rare: pneumonia, interstitial pneumonitis

8.2.1.6 Cardiac

- Rare: rapidly progressive pulmonary edema with cardiomegaly, pericarditis

8.2.1.7 Cutaneous

- Frequent: rash, alopecia (complete alopecia with high doses)

- Rare: freckling, pruritus, urticaria, skin ulceration, hand-foot syndrome, cellulitis at injection site

8.2.1.8 Nervous System

- Rare: peripheral neuritis, headache, conjunctivitis, CNS toxicity, such as encephalitis and cerebellitis (CNS complications have been described in high-dose and very high-dose cytarabine)

8.2.1.9 Metabolic

- Frequent: ASAT and ALAT
- Rare: jaundice

Cytarabine may be used intrathecally. The toxicities of intrathecal medication are roughly the same as for intravenous use. Toxicity is, however, self-limiting. Neurologic complications include paraplegia, necrotizing leukoencephalopathy, blindness, and spinal cord necrosis.

Cytarabine displays teratogenic effect in animal models. Women of childbearing age should be advised against conceiving a child during cytarabine therapy. An effective contraceptive method is recommended in both men and women.

8.2.2 Idarubicin

Idarubicin [1, 2, 11–13], an anthracycline-type topoisomerase II inhibitor, has been recommended in combination with other drugs for the treatment of acute myeloid leukemia.

The main side effects of idarubicin treatment involve hematologic toxicity. Severe myelosuppression is a constant and requires treatment with transfusions and granulocyte colony-stimulating factors. Severe febrile neutropenia may result from idarubicin-containing regimens. Idarubicin should be used with extreme caution in patients displaying cytopenias resulting from prior chemotherapies, as cases of permanent bone marrow suppression have been described.

Alopecia is a frequent complication of idarubicin-based chemotherapies.

Cardiac side effects occur frequently and mostly result from restrictive cardiomyopathy with a decline in left ventricle ejection fraction (LVEF). Decline of LVEF depends on the cumulative dose and the age of the patients. Caution should be applied in patients with preexisting cardiomyopathy or in patients who have been treated with anthracyclines previously.

Extravasation of anthracyclines may lead to extended skin necrosis, which may require surgery. In case of extravasation, intermittent cold packs should be applied and surgical advice should be taken.

Secondary neoplasias have been attributed to anthracyclines.

Side effects of idarubicin are as follows:

8.2.2.1 Hematologic

- Severe myelosuppression

8.2.2.2 Gastrointestinal

- Frequent: grades I–III nausea, vomiting, mucositis abdominal pain, and diarrhea; grade IV complications are seen in less than 5% of patients.
- Rare severe enterocolitis with perforation.

8.2.2.3 Dermatologic

- Frequent: alopecia.
- Occasional: rash, urticaria, and bullous erythrodermous rash of palms and soles. Dermatologic reactions are seen more frequently in patients receiving concurrent antibiotic therapy or with a history of radiotherapy.

8.2.2.4 Cardiac

- Congestive heart failure and serious arrhythmias, including atrial fibrillation and myocardial infarction

8.2.2.5 Neurologic

- Very rare (<5%): peripheral neuropathy, seizures, cerebellar palsy

8.2.2.6 Pulmonary

- Pneumonitis in less than 5% of patients

8.2.3 Daunorubicin

Daunorubicin [1, 2, 11, 12] is an intravenous anthracycline that is used in combination with other drugs for the treatment of acute myeloid leukemia.

Side effects of daunorubicin are roughly the same as for idarubicin. Oral mucositis, bone marrow depression, and decrease in left ventricular function, however, seem less severe than with idarubicin in patients older than 60 years of age.

The maximal cumulative dose of daunorubicin is 550 mg/m^2. Some authors propose the dose of 400 mg/m^2 in patients who have undergone radiotherapy encompassing the heart.

8.2.4 Amsacrine

Amsacrine [1, 2, 14] has been approved for the salvage treatment of AML resistant to anthracyclines. In some European countries, amsacrine is used in the consolidation of AML.

Toxicity of amsacrine is essentially hematologic, resulting in constant pancytopenia requiring supportive treatment with red blood cell transfusion and platelet

transfusion as well as granulocyte colony-stimulating factor. Amsacrine should not be used if the patient has previous profound chemo-induced pancytopenia.

Gastrointestinal toxicity is frequent and ranges from simple diarrhea to grade IV neutropenic colitis.

Cardiologic side effects consist mostly of arrhythmias, which can be triggered by coexisting hypokalemia. Close monitoring of the electrocardiogram and of serum kalium levels is recommended if using amsacrine.

The side effects of amsacrine are as follows:

8.2.4.1 Hematologic

- Very frequent: pancytopenia
- Frequent: febrile neutropenia
- Rare: major hemorrhage

8.2.4.2 Gastrointestinal

- Frequent: grade I–II nausea or vomiting, grade I–IV mucositis

8.2.4.3 Renal

- Rare: renal dysfunction, anuria, acute renal failure

8.2.4.4 Hepatic

- Elevation of serum liver tests, hyperbilirubinemia requiring dose adaptation

8.2.4.5 Neurologic

- Grand mal seizures in heavily pretreated patients with preexisting neurologic conditions

8.2.4.6 Cardiac

- Frequent: congestive heart failure, cardiac arrest, ventricular tachycardia

8.2.4.7 Cutaneous

- Reactions at injection site ranging from simple rash to necrosis

Amsacrine has proven teratogenic in mice. Effective methods of contraception are recommended in both men and women.

8.2.5 Clofarabine (Intravenous)

Clofarabine [1, 2, 15–17], a purine nucleoside analogue, has been approved in the treatment of pediatric ALL. Some studies indicate a benefit in progression-free survival in combination treatment with other drugs in relapsed AML.

Toxicity is mainly hematologic, with febrile neutropenia occurring in about a half of the patients.

Gastrointestinal toxicity is frequent and may lead to severe abdominal pain in 35% of the patients.

Palmoplantar erythrodysesthesia is a common occurrence and requires topical steroids or topical NSAIDS. Systemic corticosteroids have been discussed as prophylactic treatment.

The side effects of clofarabine are as follows:

8.2.5.1 Hematologic
- Frequent: bone marrow depression

8.2.5.2 Cardiologic
- Tachycardia in about a third of the patients
- Pericardial effusion in 35% of patients

8.2.5.3 Gastrointestinal
- Frequent: nausea, diarrhea, and vomiting in more than half of the patients. Abdominal pain occurs in 35% of patients.
- Occasional: sore throat, constipation.

8.2.5.4 General Disorders
- Fatigue pyrexia and rigors in more than one-third of the patients.
- Mucositis in 17% of patients.
- Anorexia occurs in 30% of patients.

8.2.5.5 Hepatobiliary
- Occasional: jaundice, hepatomegaly

8.2.5.6 Infectious
- Bacteremia, cellulitis, candidiasis, bacterial, and fungal pneumonia

8.2.5.7 Neurologic
- Headaches in 44% of patients
- Rare: somnolence, tremor, depression, anxiety

8.2.5.8 Respiratory
- Frequent: epistaxis
- Rare: respiratory distress, pleural effusion, cough

8.2.5.9 Cutaneous
- Frequent: dermatitis, petechiae
- Palmar planter erythrodysesthesia syndrome

8.2.6 Mylotarg (Intravenous)

Mylotarg [1, 2, 18, 19] is a monoclonal anti-CD33 antibody (gemtuzumab) linked to ozogamicin. It has been used as single-agent treatment of elderly patients with CD33-positive AML. Gemtuzumab ozogamicin has been withdrawn from the market owing to an unfavorable risk-benefit ratio.

Acute infusion-related adverse reactions occur frequently and have led in some cases to grade IV adverse events. Frequent (>30% of patients) side effects are fever, nausea, chills, vomiting, and headache. About 20–30% of patients experience dyspnea, hypotension, or hypertension, in some cases with hemodynamic instability. Less frequent acute side effects upon injection may be hyperglycemia and hypoxia. Although no antibodies to gemtuzumab have been detected to date, some severe allergic reaction has been described. Two patients have developed antibodies against ozogamicin.

Hematologic toxicity results in profound neutropenia with a mean time to recovery of 40–43 days. Anemia and thrombocytopenia are longer lasting. Median time to recovery is 50–56 days.

Hepatotoxicity is an issue in about one-third of patients undergoing treatment with gemtuzumab and ozogamycin and results in grade III–IV elevation of liver enzymes or hyperbilirubinemia. Veno-occlusive disease is a well-known but rare side effect of treatment with gemtuzumab and ozogamycin, occurring in about 1% of patients. Most cases, however, have been described in the context of allogeneic stem cell transplantation.

The delayed side effects are as follows:

8.2.6.1 Hematologic

- Very frequent: grades III–IV neutropenia.
- Anemia and thrombocytopenia.
- More than 13% of patients experienced grades III–IV bleedings.

8.2.6.2 Infectious

- Frequent: septic shock, pneumonia
- Rare: stomatitis, herpes simplex

8.2.6.3 Hepatotoxicity

- Grade III–IV increase of liver enzymes or hyperbilirubinemia
- Rare: ascites
- Veno-occlusive disease

8.2.6.4 Gastrointestinal

- Frequent: constipation, anorexia, dyspepsia, nausea stomatitis

8.2.6.5 Metabolic

- Frequent: hypokalemia
- Occasional: hyperglycemia, hypocalcemia
- Rare: hypomagnesemia, hypophosphatemia

8.2.6.6 Respiratory

- Frequent (>20%): cough, dyspnea, epistaxis
- Occasional (20–30%): pneumonia, pharyngitis

8.2.6.7 Cutaneous

- Rare: pruritus, rash

8.3 Chronic Myeloproliferative Diseases

The drugs used here are the most common ones for polycythemia vera, essential thrombocythemia, and chronic myeloid leukemia. For the latter disease, a compilation of the side effects is given in a tabulated form.

8.3.1 Hydrea

Hydroxyurea [1, 2, 20–22] is an oral inhibitor of nucleoside reductase and is widely used in melanoma, resistant chronic myeloid leukemia, recurrent carcinoma of the ovary, and myeloproliferative diseases (essential thrombocythemia, polycythemia vera).

Bone marrow toxicity is the major side effect of hydroxyurea. Treatment should not be initiated in patients displaying marked bone marrow depression. Recovery from leukopenia and thrombocytopenia is rapid after interruption of treatment.

Cutaneous toxicities are rare but may lead to skin ulcers. The development of ulcers requires interruption of hydroxyurea treatment.

In patients treated with hydroxyurea for myeloproliferative syndromes, the rate of secondary leukemias seems slightly increased.

Side effects of hydroxyurea treatment are the following:

8.3.1.1 Hematologic

- Frequent: neutropenia, thrombocytopenia, megaloblastic anemia

8.3.1.2 Cutaneous

- Exacerbation of postirradiation erythema in previously irradiated patients.
- Rare: vasculitic toxicities, ulceration, and gangrene are seen in patients with myeloproliferative disease with a history of interferon.
- Rare: dermatomyositis-like skin changes, maculopapular rash.
- Very rare: alopecia.

8.3.1.3 Renal

- Dysuria.
- Impairment of renal tubular function with hyperuricemia and increase of creatinine levels. Renal insufficiency should require dose reduction.

8.3.1.4 Gastrointestinal

- Pancreatitis has been described in patients treated with didanosine or stavudine.
- Occasional: stomatitis, nausea, vomiting, diarrhea, constipation.

8.3.1.5 Neurologic

- Rare: dizziness, headache, hallucinations, convulsions

8.3.1.6 Pulmonary

- Very rare: pulmonary fibrosis

8.3.1.7 Carcinogenesis

- Secondary leukemias have been described in patients receiving long-term treatment.

8.3.1.8 Laboratory

- Spurious gamma-GT elevations are observed, probably without any clinical consequences.

Multiple fetal malformations have been described in animal models. Men and women considering childbirth should be reassessed for the utility of their treatment, and treatment should be interrupted whenever possible.

8.3.2 Anagrelide

Anagrelide [1, 2, 22–24] is used in essential thrombocythemia to reduce platelet levels.

The main side effects of anagrelide are cardiologic and consist of supraventricular tachycardia. Anagrelide should be used with caution in patients with preexisting heart disease and prescribed only if the potential benefit outweighs the risks.

Interstitial lung disease (allergic alveolitis, eosinophilic pneumonia, and interstitial pneumonitis), though a very rare occurrence, has been associated with anagrelide. Time of onset is between 1 week and several years after initiation of therapy.

Side effects of anagrelide are the following:

8.3.3 Hematologic

- Very rare (1–5%): anemia, leukopenia, and thrombocytopenia<100,000/uL. Thrombocytopenia recovers after treatment discontinuation.

8.3.3.1 General
- Frequent (20–30%): asthenia
- Occasional (10–20%): dizziness, pain, fever
- Rare (5–10%): malaise
- Very rare (<5%): flu-like symptoms, chills, photosensitivity, thromboses

8.3.3.2 Cardiac
- Frequent (20–30%): palpitations, edema
- Rare (5–10%): tachycardia
- Very rare (<5%): arrhythmia, hypertension, orthostatic hypotension, angina pectoris, heart failure

8.3.3.3 Pulmonary
- Interstitial lung diseases

8.3.3.4 Locomotor
- Very rare: arthralgia, myalgia, cramps

8.3.3.5 Cutaneous
- Rare (5–10%): pruritus
- Very rare (<5%): alopecia

8.3.3.6 Gastrointestinal
- Occasional (10–20%): nausea, abdominal pain, flatulence
- Rare (5–10%): vomiting
- Very rare (<5%): GI hemorrhage, melena, aphthous stomatitis, constipation

8.3.3.7 Special Senses
- Very rare (<5%): amblyopia, abnormal vision, tinnitus, diplopia, visual field abnormality

Some cases of pregnancies occurring while on anagrelide treatment have been described with no fetal harm. It is, however, recommended that treatment be stopped during pregnancy or if there is a desire to conceive.

8.3.4 Tyrosine Kinase Inhibitors in CML [1, 2, 25–27]

Tyrosine kinase inhibitors are indicated in the treatment of CML. In first-line treatment, imatinib has changed the prognosis of CML. In recent years, nilotinib and dasatinib, two second-generation tyrosine kinase inhibitors, have been licensed in first-line treatment of CML. Imatinib and dasatinib have shown efficacy in GIST. Hypereosinophilic syndromes displaying FIP-1L1PDGFR-alpha translocation are also responsive to imatinib.

Table 8.1 Comparative side effects of current tyrosine kinase inhibitors

	Frequency					
	Imatinib[a]		Nilotinib[b]		Dasatinib	
Side effects	All grades	Grade III–IV	All grades	Grade III–IV	All grades	Grade III–IV
Hematologic side effects (%)						
Neutropenia	58–68	20	38–43	10–12	65	21
Thrombocytopenia	56–62	9–10	48	10–12	70	19
Anemia	47–84	5–7	38–47	3	90	10
Nonhematologic side effects (%)						
Peripheral edema	14–36	0	5	0	9	0
Eyelid edema	13	<1	2–5	<1	0	0
Pleural effusion	0	0	0	0	19	1
Periorbital edema	34	0	1–2	0	0	0
Diarrhea	17–60	1	18–22	1	17	<1
Nausea	20–31	0	32–54		8	0
Vomiting	10–14	0	5–9	1	5	0
Myalgia	10–12	0	10	0	6	0
Muscle inflammation	17	<1	NA	NA	4	0
Muscle pain	14–24	<1	6–7	0	11	0
Rash	11–17	1	31–36	1–3	11%	0
Headache	8–10	0	14–21	1	12	0
Fatigue	8	<1	9–11	0–1	10	0
Alopecia	11	0	22–36	0	0	0
Metabolic side effects (%)						
Increased bilirubin	10	<1	53–62	4–8	NA	
Increased alkaline phosphatase	33	<1	21–27	0		
Hypophosphatemia	45	8	32–34	5		
Hyperglycemia	20	0	41–36	4–6		
Increased lipase	11	3	24–29	6		
Increased amylase	12	<1	15–18	1		
Increased ALT	20	2	66–73	4–9		
Increased AST	23	1	40–48	1–3		
Increased creatinine	13	<1	5	0		

Adapted from [25, 26]

[a]Ranges for imatinib depend on the study analyzed

[b]Ranges for nilotinib depend on the dosage (300 or 400 mg)

The spectrum of side effects is comparable between imatinib, dasatinib, and nilotinib. However, the frequency of the respective side effects varies from one molecule to another and may influence treatment decision. Table 8.1 compares the major side effects of the three molecules.

In 2011, a warning was issued by the FDA concerning the risk of pulmonary hypertension in patients receiving dasatinib. Caution is recommended in patients with previous pulmonary hypertension. Close monitoring by cardiac ultrasound is recommended.

Bosutinib, a third-generation tyrosine kinase inhibitor has been licensed for the treatment of relapsed or refractory CML. The most frequent side effects are hematological side effects: Neutropenia, thrombocytopenia, and anemia will require halting of the medication and adaptation when the hemogram returns to normal. Fluid retention is a common side effect as with other tyrosine kinase inhibitors. Arrhythmia with risk of QT prolongation will require ECG testing at the beginning of the treatment and careful assessment with other medication at risk to prolong QT (macrolides, triazoles).

Ponatinib is a tyrosine kinase inhibitor effective in patients displaying the T315I mutation of bcr-abl. Its license has been reviewed after several arterial events had been described. It appears that patients presenting at least one risk factor for arterial disease are at higher risk of developing peripheral arterial obstruction or ischemic heart disease if treated with ponatinib.

The arterial risk does not seem restricted to ponatinib alone, but bosutinib, nilotinib, and to a lesser extent dasatinib have also an increased risk of inducing arterial disease in presence of one or more risk factors. Careful assessment of risk factors should therefore be recommended before and during the treatment.

8.3.5 Ruxolitinib [28, 29]

Ruxolitinib, a nonselective Jak-2 inhibitor, has demonstrated its efficacy in the treatment of general symptoms of myelofibrosis. Patients under ruxolitinib experience rapid decrease in spleen size and reduction of general symptoms leading to an enhanced quality of life. Ruxolitinib decreases the Jak-2 burden in a small subset of patients.

Main toxicities are:

Hematologic:

- Thrombocytopenia and anemia: Frequent starting dose should be reduced in presence of a thrombocytopenia <100,000/ul and dosages withheld until correction in case of thrombocytopenia<50,000.

Infections:

- Infections occur in up to 50% of patients in the first weeks and consist mainly of pneumonia urinary tract infections: in the COMFORT-II trial, the incidence of infections tended to be maximal in the first weeks of treatment and falls to 30% after 6 months.
- Risk of hepatitis B virus reactivation has recently been reported.

Bleeding

- Bleeding (epistaxis hematomas) is frequent (around 17%) in the first weeks of trials and recedes after 6 months of treatment.

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Lymphoma

9

Sigrid Cherrier-De Wilde

Abstract

Lymphomas are subdivided in Hodgkin's disease (HD) and non-Hodgkin's lymphomas (NHL). Essentially the medications used are of two types: monoclonal antibodies and chemotherapy. The side effects of treatment are grouped accordingly. The most commonly used treatment protocol in NHL is a combination of a monoclonal antibody with polychemotherapy. Hence, this chapter is subdivided according to these two treatment modalities.

Keywords

Hodgkin's disease · Non-Hodgkin's lymphomas · Chemotherapy · Monoclonal antibodies

9.1 Introduction

Lymphoma has multiple subtypes. It is variable in its histopathology, symptomatology, area of involvement, and prognosis and treatment. Lymphoma represents about 5% of cancers and more than 55% of hematologic cancers.

Lymphomas are divided into two groups: the Hodgkin's and the non-Hodgkin's lymphomas. However, sometimes, it is not possible to classify lymphoma in one of those groups; these cases are labeled B-cell lymphoma unclassifiable.

The classical chemotherapy schedule for a non-Hodgkin's lymphoma is the CHOP (cyclophosphamide, hydroxorubicin, Oncovin, and prednisone) regimen and its derivatives (CVP, CHOEP, COMP, etc.), but purine nucleoside-based combinations are also possible.

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M. A. Dicato, E. Van Cutsem (eds.), *Side Effects of Medical Cancer Therapy*,
https://doi.org/10.1007/978-3-319-70253-7_9

More intensive schedules include ifosfamide, platins, cytarabine, and melphalan.

Treatment of lymphoma is based on a combination of chemotherapy, radiotherapy, and monoclonal antibodies or a monotherapy with either one of them.

In case of relapse or even for high-grade lymphomas in first remission, an intensification of the treatment can be done by means of high-dose chemotherapy followed by the infusion of stem cells. Mostly these are autologous stem cells, but allografting is a therapeutic option for a relapsing lymphoma.

On the other hand, there is also the treatment of secondary manifestations like pain, hypercalcemia, hyperuricemia, spontaneous tumor lysis, spinal cord compression, seizures, renal insufficiency, anemia, thrombocytopenia, and so forth. These aspects are covered in other chapters of this book.

Lymphomatous meningitis is treated by high-dose intravenous chemotherapy (cytarabine or methotrexate) and intrathecal chemotherapy (methotrexate, cytarabine, hydrocortisone). More novel treatments include, for example, intrathecal rituximab.

9.2 Monoclonal Antibodies [1–5]

9.2.1 Rituximab

Rituximab is one of the most commonly used intravenous drugs in the treatment of CD20-positive lymphomas.

The possibility of severe or even fatal infusion reaction necessitates the use of adequate premedication (antipyretics, antihistamine, and glucocorticoid). Resuscitation equipment should be available, and close monitoring is indispensable, especially in patients with a preexisting cardiac condition.

The initial infusion rate (250 mg/h) has to be increased every 30 min to a maximum of 400 mg/h. If a severe reaction happens, stop immediately. In case of a less severe reaction, the diffusion rate is to be decreased.

Tumor lysis syndrome occurs frequently when there is a large tumor burden and necessitates adequate hydration, rasburicase, or allopurinol.

Because of suppression of the B lymphocytes with increased sensitivity to infections, prophylaxis against pneumocystis and herpes may be necessary.

The most frequent side effects are fever, hypertension, peripheral edema, pain, rash, pruritus, nausea, diarrhea, cytopenia, arthralgia, cough, and weakness.

Less frequent adverse events include hypotension, anxiety, dizziness, hyperglycemia, progressive multifocal leukoencephalopathy (JC virus), bowel obstruction and perforation, ventricular tachycardia, viral reactivation, and mucocutaneous reactions.

Drug interactions with anticoagulants or antiplatelet agents, immunosuppressants, vaccines, and so forth need to be considered.

In order to prevent pregnancy, effective contraceptive methods, as discussed in another chapter in this book, are recommended during and for a minimum of 12 months following therapy.

9.2.2 Ibritumomab (Zevalin)

Ibritumomab is an intravenous radioimmunotherapy for CD20-positive lymphomas in relapsed or refractory setting or as a part of intensification.

The necessary premedication is similar to that for rituximab, and serious fatal infusion reactions may occur (see Sect. 9.2.1).

No administration should be considered if the platelets are below 100,000 cells/mm^3 or in case of 25% bone marrow involvement because of the risk of prolonged cytopenia.

The most frequent side effects are fatigue, chills, fever, pain, headache, nausea and vomiting, diarrhea, abdominal pain, nasopharyngitis, cough or dyspnea, infection, and hematologic toxicity.

Less frequent adverse reactions occur as peripheral edema, hypertension or hypotension, flushing, pruritus, rash, myalgia or arthralgia, melena, myelodysplastic syndromes, bronchospasm, and apnea.

There is a risk of formation of human anti-mouse antibodies (HAMA).

Severe mucocutaneous reactions or extravasation and radiation necrosis are possible.

Delayed radiation injury in the region of lymphoma can occur.

One should pay attention to drug interactions with anticoagulants or antiplatelet agents, immunosuppressants, and vaccines.

The B-cell recovery starts only at 3 months and reaches normal range in 9 months.

9.2.3 Alemtuzumab

Alemtuzumab is an intravenous or subcutaneous drug with the following action: antibody-dependent lysis by binding the CD52 of B-cell chronic lymphocytic leukemia (CLL), T-cell lymphoma, and T-cell prolymphocytic leukemia.

In the beginning, dose escalation is required. Because of a possible infusion reaction, it is necessary to initiate effective antiallergic and antipyretic treatment before administration. There is a high infection rate if no prophylactic treatment is administered.

In case of subcutaneous injection, a local site reaction can be observed.

The most frequent side effects are hypotension, peripheral edema, hypertension, dysrhythmias, fever, fatigue, headache, dizziness, rash, urticaria and dizziness, nausea and vomiting, anorexia, rigors, myalgias, and skeletal pain.

Less frequent side effect reactions include chest pain, purpura, dyspepsia, positive Coombs' test without hemolysis, autoimmune thrombocytopenia, and hemolytic anemia.

A serious and fatal cytopenia can occur, and transfusion with irradiated blood product is recommended because of the potential for graft-versus-host disease (GVHD) during lymphopenia.

9.2.4 Obinutuzumab

Obinutuzumab [6] is an intravenous anti-CD20 antibody and is used for CLL, CD20-positive lymphomas.

Despite a premedication with acetaminophen, antihistamine, and glucocorticoid, a severe infusion reaction can happen: bronchospasm, laryngeal edema, flushing, headache, and dyspnea. The infusion must be interrupted and or the rate reduced, after a life-threatening grade 4 infusion reaction, obinutuzumab should be permanently discontinued.

Prevention for tumor lysis syndrome with hydration and antihyperuricemic prophylaxis is necessary. There is no dose adjustment for renal nor hepatic impairment.

All patients should be screened for hepatitis B virus infection before initiation of obinutuzumab and HBV-positive patients be monitored. In case of HBV reactivation, obinutuzumab must be discontinued.

The most frequent adverse events are hypocalcemia, hyperkaliemia, hypoalbuminemia, hyponatremia, leukopenia, thrombocytopenia, anemia, infections, hepatic alterations, etc.

Less frequent side reactions can occur such as progressive multifocal leukoencephalopathy, hypertension or hypotension, hyperphosphatemia, diarrhea or constipation, exacerbation of cardiac disease, back pain, etc.

9.2.5 Ofatumumab

Ofatumumab [7] is a new intravenous drug for relapses of CD20-positive lymphomas and leukemias after treatment with rituximab.

There is no dosage adjustment in case of renal or hepatic impairment.

The possible adverse effects are flu-like signs, fatigue, skin rash, nausea, diarrhea, infections, cough, temperature, mouth sores, anal itching, peripheral edema, and difficulty speaking.

Like the other anti-CD20 antibodies, there is a risk for infusion reaction, tumor lysis syndrome, HBV reactivation, PML, etc.

Women of childbearing potential should not become pregnant during and up to 6 months after last administration of ofatumomab, what also me be excreted in breastmilk.

9.2.6 Tositumomab

Tositumomab is an intravenous radioimmunotherapeutic drug acting on depletion of CD20-positive cells by apoptosis, complement-dependent cytotoxicity, and antibody-dependent cellular cytotoxicity.

As for rituximab administration, premedication is necessary to avoid infusion-related toxicity.

The administration of thyroid-protective agents is recommended 24 h before administration of the dosimetric dose.

The most frequent adverse events are fever, pain, chills, headache, rash, hypothyroidism, nausea, anorexia, myelosuppression, myalgia, cough, dyspnea, and infections.

Less frequent side reactions can occur as hypotension, peripheral edema, dizziness, pruritus, arthralgia, rhinitis, and secondary malignancies.

Tositumomab should not be used in patients with impaired bone marrow reserve or marrow involvement over 25%.

9.2.7 Temsirolimus

Temsirolimus is an intravenous mTOR kinase inhibitor in the treatment of mantle cell lymphoma.

Premedication with an H1 antagonist is indispensable. In case of a hypersensitivity reaction, the infusion rate should be slowed.

Drug interactions and concomitant administration of CYP3A4 inhibitors or inducers as well as anticoagulants and sunitinib should be avoided. The patient should also avoid drinking grapefruit juice.

This drug is contraindicated in moderate to severe hepatic dysfunction.

The dose must be adapted for hematologic toxicity. The dose may need to be adapted to the complete blood count.

The most frequent adverse reactions are edema, chest pain, fever, headache, insomnia, rash, hyperglycemia, hypercholesterolemia, hypophosphatemia, hypokalemia, mucositis, nausea and anorexia, diarrhea, dyspnea, and infections.

Less frequent side effects are hypertension, venous thromboembolism, depression, acne, bowel perforation, hyperbilirubinemia, myalgia, interstitial lung disease, and seizure.

To prevent pregnancy, effective contraceptive methods for men and women during and for a minimum of 3 months following therapy are recommended for all the aforementioned drugs.

9.2.8 Brentuximab Vedotin [8]

This is an antibody drug conjugate with anti-CD30 properties, used for refractory Hodgkin lymphoma and systemic anaplastic large cell lymphoma or as maintenance therapy after autologous hematopoietic stem cell transplantation.

The dose must be adapted for mild hepatic impairment and not used for Child-Pugh class B or C. Avoid use in patients with severe renal impairment (CrCl <30 ml/min).

The most common side effects are peripheral neuropathy, pulmonary toxicity, fatigue, headache, dizziness, diarrhea, neutropenia, hepatotoxicity, Stevens-Johnson syndrome or toxic epidermal necrolysis, anaphylaxis or infusion reaction, PML, etc.

Brentuximab should not be used in association with bleomycin because of increase of pulmonary toxicity.

The microtubule-disrupting agent monomethyl auristatin E of the drug may cause fetal harm if administered to a pregnant woman.

9.2.9 Lenalidomide

Lenalidomide [9, 10] is a thalidomide analogue with antineoplastic, immunomodulatory, and antiangiogenic characters.

Because of the known human teratogenicity, it is only available under a restricted distribution program controlling pregnancy tests and contraception.

It is used for myeloma, mantle cell lymphoma, myelodysplastic syndrome with deletion 5q, chronic lymphatic leukemia, systemic light-chain amyloidosis, etc.

Dose of lenalidomide must be adapted to renal function and age.

Lenalidomide for more than four cycles may reduce the facility to collect stem cells. So, the optimal time for stem cell collection must be defined and an eventual combination with cyclophosphamide or CXC chemokine receptor 4 inhibitor proposed.

The most dangerous risks are deep vein thrombosis and pulmonary embolism, neutropenia and thrombocytopenia, tumor flare reaction, skin rash, and angioedema.

Other side effects are edema, fatigue, insomnia, dizziness, depression, neuropathy, hypothyroidism, diarrhea, constipation, second primary malignant neoplasms, muscle cramps, back pain, blurred vision, etc.

9.3 Chemotherapy [2, 11]

9.3.1 Fludarabine

Fludarabine [12–14] is a widely used oral and intravenous purine analog in cases of CLL, acute leukemia, follicular lymphoma, Waldenström's macroglobulinemia, and stem cell transplant.

An adjustment to renal creatinine clearance must be made.

A major problem can be hematotoxicity, with even very long cytopenias (2 months to 1 year) and common autoimmune effects such as hemolysis, ITP, Evans syndrome, and acquired hemophilia. These side effects may recur if the patient is given the drug again.

Because of the frequent opportunistic infections, prophylactic anti-infectives should be considered.

The most frequent adverse reactions are edema, fever, fatigue, rash, nausea, diarrhea, neuromuscular weakness, visual disturbance, paresthesia, cough, and pneumonia. Less frequent side effects include headache, neurotoxicity (coma, confusion, seizure, PML), arrhythmia, thromboembolic event, alopecia, hyperglycemia, stomatitis, dysuria, hearing loss, hematuria, allergic pneumonitis, flu-like syndrome, and cortical blindness.

Fludarabine should not be used in combination with pentostatin because of the risk of severe or fatal pulmonary toxicity.

If transfusion is necessary, only irradiated blood products should be used because of the possibility of transfusion-related GVHD.

The combination with alcohol can induce gastrointestinal irritation.

Drug interactions with trastuzumab, clozapine, immunosuppressants, and vaccines can occur.

In order to prevent pregnancy, effective contraceptive methods are recommended for men and women during and for a minimum of 6 months following therapy.

9.3.2 Chlorambucil

Chlorambucil is an old oral alkylator to treat CLL, non-Hodgkin's lymphoma, Hodgkin's lymphoma, and Waldenström's macroglobulinemia.

Frequent adverse events are drug fever, skin reaction (discontinue promptly), edema, syndrome of inappropriate antidiuretic hormone (SIADH) secretion, hematologic toxicity, hepatotoxicity, neuropathy, interstitial pneumonia, secondary malignancies, and seizures (especially if there is a history of seizure, nephrotic syndrome, or head trauma).

A dosage reduction is needed in case of hepatic impairment.

The absorption is reduced with food.

Drug interactions with trastuzumab, clozapine, immunosuppressants, and vaccines can occur.

It can affect human fertility and probably has mutagenic and teratogenic effects, which are covered elsewhere in this book.

9.3.3 Bleomycin

Bleomycin is an antineoplastic drug from the family of antibiotics, administered intravenously, intramuscularly, subcutaneously, and intrapleurally for a wide range of indications, such as Hodgkin's lymphoma, testicular cancer, ovarian germ cell cancer, malignant pleural effusion, and squamous cell carcinoma.

The best known toxicity is pulmonary, and this risk increases with cumulative lifetime dose (>400 mg). It is diagnosed as an interstitial pneumonitis and pulmonary fibrosis, and the response to corticoids is variable. It is more frequent in the elderly, smokers, and patients with prior radiation therapy or who are undergoing oxygen therapy. Filgrastim may enhance the adverse effects and pulmonary toxicity.

There is a risk for an anaphylactoid reaction. It is controversial whether an initial test dose should be given because of false-negative results. The onset may be immediate or delayed for several hours.

The dose must be adjusted in cases of renal impairment.

The most frequent adverse reactions are phlebitis, pain at tumor site, hyperpigmentation, alopecia, mucositis, anorexia, and acute febrile reactions.

Rare side effects include angioedema, chest pain, cerebrovascular accident (CVA), hepatotoxicity, Raynaud's phenomenon, and thrombotic microangiopathy.

Women should avoid becoming pregnant during treatment.

9.3.4 Carmustine (BCNU)

Carmustine is an intravenous alkylator for Hodgkin's lymphoma, multiple myeloma, brain tumors, non-Hodgkin's lymphoma, glioblastoma, stem cell transplant, and mycosis fungoides.

This product is an irritant at the injection site and should be prepared in glass or polyolefin containers. The infusion must go slowly for 2 h to avoid flushing, hypotension, and agitation.

The most frequent adverse events are arrhythmia, ataxia, headache, hyperpigmentation, vomiting, nausea, hematologic toxicity, hepatic toxicity, conjunctival suffusion, renal failure, interstitial pneumonitis, and pulmonary fibrosis (with delayed onset).

Melphalan favors the adverse effects and sensitizes patients to carmustine lung toxicity.

Attention needs to be paid to drug interactions with trastuzumab, clozapine, immunosuppressants, and vaccines.

Women should avoid becoming pregnant while on treatment.

9.3.5 Dacarbazine

Dacarbazine is an intravenous alkylator for Hodgkin's lymphoma, metastatic melanoma, and sarcoma.

In case of extravasation, immediately apply cold packs and protect the site of extravasation from daylight.

The most frequent adverse reactions are alopecia, nausea and vomiting, anorexia, myelosuppression, flu-like syndrome, hepatic necrosis, anaphylactic reactions, and renal and liver impairment.

One should pay attention to drug interactions with trastuzumab, clozapine, immunosuppressants, and vaccines; patients should avoid ethanol and St. John's-wort.

Because of its known carcinogenic and teratogenic effects, dacarbazine should be used in pregnancy only if the benefit outweighs the potential risk to the fetus.

9.3.6 Bendamustine

Bendamustine [4, 5, 15, 16] is an old but newly available intravenous alkylator for CLL, non-Hodgkin's lymphoma, mantle cell lymphoma, and multiple myeloma.

Its use is not recommended if moderate or severe hepatic insufficiency is present or if clearance is under 40 mL/min. Hypersensitivity reactions during infusion are possible (chills, pruritus, rash, fever, anaphylactic reactions).

The most frequent adverse events are peripheral edema, fatigue, fever, headache, chills, rash, nausea and vomiting, diarrhea, stomatitis, abdominal pain, myelosuppression, weakness, cough, and dyspnea.

Rare side effects can be tachycardia, anxiety, pain, chest pain, hypotension, xerostomia, increase in transaminases, infusion site pain, infection, and toxic skin reactions.

One should pay attention to drug interactions with clozapine and inducers or inhibitors of CYP1A2.

In case of possible pregnancy, effective contraceptive methods during and for a minimum of 3 months following therapy are recommended.

9.3.7 Bortezomib

Bortezomib [17] is an intravenous and subcutaneous proteasome Inhibitor, used for multiple myeloma, mantle cell lymphoma, cutaneous or peripheral T-cell lymphoma, follicular lymphoma, systemic light-chain amyloidosis, or Waldenström macroglobulinemia.

Bortezomib does not need dose adjustment for renal failure but should be administered postdialysis. For severe hepatic impairment, the dose must be reduced.

The risk for neuropathy is less when subcutaneous administration.

The most frequent adverse reactions are hypotension, peripheral neuropathy, fatigue, headache, skin rash, diarrhea, nausea, constipation, thrombocytopenia, herpes zoster infection or reactivation, dyspnea, exacerbation of heart failure, etc.

Patients treated with bortezomib should avoid taking vitamin C supplements, multivitamins, green tea or green tea extracts, and grapefruit juice. Males and females of reproductive potential must use effective contraception until 3 months following the treatment.

The newer upcoming proteasome inhibitors are intravenous carfilzomib and oral ixazomib.

9.4 Other Chemotherapeutic Agents

Doxorubicin, etoposide, vincristine, vinblastine, methotrexate, cytarabine, cisplatin, ifosfamide, carboplatin, and gemcitabine, they're all frequently used drugs for lymphomas. They are described in other parts of this book (myeloid disease, lung cancer, gynecological cancers).

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Multiple Myeloma

10

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Abstract

The treatment and prognosis of multiple myeloma have completely changed over the past *years* with the advent of the new non-chemotherapeutic agents like imids and proteasome inhibitors *followed by their second generations and other new drugs*. Their side effects are completely different from those seen with standard *chemotherapeutic* treatment. Some are common, like peripheral neuropathy, blood count changes, venous thromboembolic events, fatigue, and others. These different toxicity profiles allow combinations and sequences of administration, trying to avoid cumulative toxicities and increasing the treatment combinations. In the first edition of this book there were only three but important drugs. Just a few years down the road in this second edition, our armamentarium has enlarged to additional imids and proteasome inhibitors, as well as completely new drugs, being monoclonal antibodies and HDAC inhibitors, and certainly more to come including immuno-oncology drugs. Over the next few years on some of the new drugs, now used in relapsed/refractory myeloma, data will become available also in induction and maintenance therapy. It is highly probable that the explosion of indications of immuno-oncology treatments will include also multiple myeloma. The transformation two decades ago of this lethal disease into a chronic disorder is being further improved and confirmed more and more.

Keywords

Myeloma · Plasma cell dyscrasias · Side effects · Thalidomide · Lenalidomide Pomalidomide · Bortezomib · Carfilzomib · Ixazomib · Daratumumab Elotuzumab

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M. A. Dicato, E. Van Cutsem (eds.), *Side Effects of Medical Cancer Therapy*,
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10.1 Introduction

With the availability over the past 20 years of new drugs—imids, proteasome inhibitors, and monoclonal antibodies—multiple myeloma is one of the few instances in neoplastic diseases where a poor prognostic malignancy has been changed into a more chronic disease with a substantial improvement in quality of life and survival.

Before the availability of these agents, the side effects of chemotherapy were essentially and still are those of bone marrow depression, which occurs with standard- and high-dose chemotherapy, with and without autologous stem cell transplantation. Chemotherapy's side effects of anemia, neutropenia, and thrombocytopenia, as well as mucositis, hair loss, and so forth, are similar to those that occur in other oncological situations, namely, hypo-oxygenation, infections, and bleeding, and they are described elsewhere in this book.

These new nonstandard chemotherapeutic drugs have a different toxicity profile that will be covered in this chapter. For treatment of the also frequent but less pronounced and more transient standard side effects like anemia and neutropenia, it is referred to the entire coverage of these side effects in the specific chapters in this book. Various nonspecific side effects, such as constipation and fatigue, are treated symptomatically.

Of note, these second-generation and new agents may represent alternatives in treatment combinations and sequences and therefore have significantly less side effects. More drug combinations and earlier dose adaptations of and after first line therapy become possible. Also preventive measures like systematic anticoagulation have resulted in less side effects like venous thromboembolic events (VTE).

Risk management plans have been required by the regulatory authorities in order to follow closely possible risks for patients. For some medications information, booklets or leaflets are required to be given to patients in addition to mandatory forms to be signed by the treating physician and consent forms by the patient.

A caution has to be raised in attributing a specific adverse event to a single drug as often combinations are used and the hematological side effects of anemia, neutropenia, and thrombocytopenia as well as the infectious problems are mostly multifactorial, i.e., disease dependent and other previous and simultaneous therapies.

10.2 IMIDS

10.2.1 Thalidomide

Thalidomide, which was used some 50–60 years ago to treat emesis in pregnancy and as a light sedative, was taken off the market because of its major teratogenic effect of phokomelia mostly due to its antiangiogenic properties. The drug kept being used for leprosy and some other autoimmune situations. By the end of the 1990s, thalidomide became available for multiple myeloma. Very rapidly, this drug

was used fairly frequently at various dosages as a primary treatment, as maintenance, and in combination with other treatments, such as chemotherapy, corticosteroids, and with bortezomib when this product became available. Several side effects are characteristic, like peripheral neuropathy, which is a major side effect of this drug. The second major side effect is the risk of venous thromboembolic events. This complication is the same as for lenalidomide, as discussed below.

Peripheral neuropathy (PN) is one of the major side effects of this drug. The neuropathy is mostly sensorial with dysesthesias and less frequently of the motor type. Often patients with myeloma already have some neuropathic symptoms owing to the disease itself, other medical problems like diabetes or alcohol consumption, or to previous peripheral nerve-damaging treatments like vincristine, which was part of the standard VAD therapy (vincristine, Adriamycin, and dexamethasone). The precise mechanism of thalidomide-induced PN is not established. A dose-dependent neuropathy occurs frequently, and often this side effect becomes irreversible and may have a major negative impact on quality of life. EMG testing can be useful to exclude other pathologies. Early clinical diagnosis is of prime importance. One should ask the patient about early signs like dysesthesia, pain, and so forth in order to modify the dose, lengthen the interval of administration, or to stop the medication. Side effects may be alleviated by standard pain medication or gabapentin, pregabalin, and so on [1]. Vitamin B preparations have not been a major contribution to therapy.

Other less frequent side effects like psychic and cognitive disorders, cardiac toxicities, pulmonary hypertension, sexual dysfunction, and fatigue have been reported [2].

10.2.2 Lenalidomide

Lenalidomide is of the same group as thalidomide, but it has a different toxicity profile. The bone marrow toxicity of thalidomide is very minor or nonexistent, but lenalidomide may present major hematologic toxicity.

Neutropenia is common with lenalidomide when given as single agent, as, for instance, in maintenance therapy. However, the incidence of neutropenia is notably increased when lenalidomide is used in combination with chemotherapeutic agents [1]. Febrile neutropenia, on the other hand, is less frequent. Neutropenia may be such that treatment will have to be adapted, the more so when used in association with chemotherapeutic agents.

Secondary cancers like myelodysplastic syndromes (MDS) and acute myeloid leukemia (AML) have been reported in about 6% of patients, with an expected 2% in the placebo group [3, 4]. The interpretation of this observation is difficult, however. Of note, the same malignancies, MDS and AML, are also increased in untreated monoclonal gammopathies of unknown significance [3, 4]. For thalidomide, no increased risk has been reported [5].

Venous thromboembolic events (VTE) are reported with both thalidomide and lenalidomide. The incidence is markedly increased if patients are treated in

combination with a corticosteroid, mostly dexamethasone, erythropoietin, and/or a chemotherapeutic agent. In these situations, the standard prophylaxis set forth and singled out specifically in all guidelines for VTE in cancer patients is recommended [6]. In addition to these recommendations, it is notable that prophylaxis with aspirin is useful and can be an option [7]. Skin rashes are seen occasionally with lenalidomide. Symptomatic treatment is advisable. Often dexamethasone can be added as anti-myeloma therapy, and skin rashes may be controlled.

Lenalidomide does not have peripheral neuropathy as a side effect and can be an alternative to thalidomide or bortezomib [8]. Renal failure can be induced or worsened by lenalidomide. A rare renal complication is *acute interstitial nephritis*. A renal biopsy is necessary to diagnose this complication because in myeloma, renal failure can be present due to other causes. Often myeloma patients are on bisphosphonates, including zoledronic acid; these possibly nephrotoxic agents are covered in another chapter in this book. With these agents, accompanying lesions are tubular necrosis and not interstitial nephritis. In lenalidomide-induced interstitial nephritis, some authors presume the cause is immune mediated [9].

10.2.3 Pomalidomide

Pomalidomide is a second-generation imid used mostly in refractory/relapsed myeloma with mostly grade 3–4 hematological toxicity profile (anemia, neutropenia, and thrombocytopenia). The incidence of febrile neutropenia can be important in up to 10%. Non-hematological grade 3–4 adverse events are pneumonia, bone pain, and fatigue. Peripheral neuropathy is not of any significance. These are observed clinical situations, and as with all other drugs given in combination, it is difficult to attribute an adverse event specifically to one of the medications. In the reported trials, the incidence of VTE is rather low as protocols require patients to have preventive anticoagulation [10].

10.3 Proteasome Inhibitors

10.3.1 Bortezomib

This proteasome inhibitor, first in class, has also been a major advance in treatment of myeloma. Side effects include also peripheral neuropathy (PN). Usually PN is less severe than the one seen with thalidomide, and if the medication is stopped when not far advanced, this side effect is mostly reversible.

As with thalidomide, questioning the patient and paying attention to early clinical signs of dysesthesia can be helpful.

One major side effect is *thrombocytopenia*. This is not due to bone marrow toxicity, as seen with chemotherapeutic agents, but is a transient effect on platelet release

by megakaryocytes. It is advisable to stop or decrease the dosage when platelet levels are below 50,000 mm^3; however, platelet transfusions are rarely necessary.

Herpes zoster-varicella virus reactivation can occur with bortezomib and increase the incidence of debilitating postherpetic neuralgia, especially when bortezomib is used in combination with high-dose dexamethasone. Acyclovir has to be considered as a prophylactic measure [11].

Renal insufficiency is a frequent complication of myeloma. The incidence is about 20–40% at presentation and can be 50% or more in the course of the disease. Renal failure can be induced or worsened with nonsteroidal anti-inflammatory drugs or bisphosphonates. Bortezomib, through its rapid anti-myeloma effect has been shown to improve kidney function and may sometimes prevent or even reverse dialysis [12]. If for some reason bortezomib is not indicated, thalidomide or lenalidomide can be an option [13].

10.3.2 Carfilzomib

Carfilzomib is a second-generation proteasome inhibitor. Like the other proteasome inhibitors bortezomib and ixazomib, anemia, neutropenia, and thrombocytopenia are the most frequent, transient side effects with a variable incidence of 5–30% depending on the combination schedule used. Peripheral neuropathy is not frequent, much less than with bortezomib.

10.3.3 Ixazomib

Ixazomib is an interesting proteasome inhibitor due to the fact that it is an orally administered drug and hence in combination with an imid and a corticosteroid an "all oral combination" becomes available. Patients become less health system dependent, and it is important to control drug compliance. The toxicity profile is very similar to carfilzomib with hematological side effects and a low incidence of neuropathy.

Other proteasome inhibitors including oral formulations are in various clinical trials and might become available within a few years.

10.4 Monoclonal Antibodies

The classical three pillars of the newer non-chemotherapy drugs have been imids, proteasome inhibitors and corticosteroids, essentially dexamethasone. Over the past few years, the treatment armamentarium of myeloma has further improved by the availability of monoclonal antibodies, an additional group of drugs. As of now, two are marketed and part of myeloma therapy, being daratumumab and elotuzumab. Others are in early clinical trials.

10.4.1 Daratumumab

Before the first administration of daratumumab, it is important to determine blood grouping and the presence of irregular antibodies (indirect Coombs testing). "Type and screen" before first administration!

Daratumumab links to CD38 present on red blood cell (RBC) surface and can induce a positive indirect Coombs test. Linking of daratumumab to RBCs can mask irregular antibody testing present in patient's serum. Adding Coombs' reagent, its antibodies link to daratumumab and give a false positive indirect Coombs test interfering with blood compatibility testing. Daratumumab does not affect the determination of ABO/Rhesus blood grouping. In case of emergency, ABO-/Rh-typed compatible RBCs without cross-matching can be given according to local practice. So far it seems that no significant hemolysis has occurred in patients on daratumumab and no transfusion reaction after transfusion of RBCs. This false indirect Coombs test can persist for 6 months beyond usage of daratumumab. All patients need to be informed about this fact and instructed to carry an information card to present to medical professionals. If a patient needs RBCs and had daratumumab in the preceding year, it is necessary to inform the blood bank.

Infusion reactions are frequent, of grade 1–2 in up to 70% of patients, mostly during the first infusion. This frequency is lower in schedules of longer duration of administration. Stressing the importance of the infusion rate, most of these side effects can be reduced. Grade 3–4 side effects of more than 10% other than infusion reactions, attributable to daratumumab, and different from the various comparator arms also including lenalidomide or bortezomib were neutropenia, diarrhea, upper respiratory infection, and cough [14, 15]. Less frequent adverse events were pneumonia, fatigue, nausea, and dyspnea [16].

10.4.2 Elotuzumab

Elotuzumab is a monoclonal antibody targeting signaling lymphocyte activation molecule SLAMF7, a glycoprotein expressed on plasma cells. Elotuzumab has a dual effect on SLAMF7 and in addition by activating antibody dependent cytotoxic cells (ADCC) and directly NK cells.

Compared to patients in control groups a significant difference of grade 3–4 side effects were noted for neutropenia, lymphopenia, and herpes zoster infections. Ten percent of patients had grade 1–2 infusion reactions like fever, chills, hypertension, fatigue, cough, headache, nausea, and back pain, mostly with the first dose and significantly reduced by premedication. No peripheral neuropathy has been attributed to elotuzumab. Antidrug antibodies were noted in up to 15% of patients [17]. According to manufacturer's labeling as of now, no dose adjustments are required in renal or in hepatic impairment. Secondary malignancies (solid tumors and skin cancer) have been noted more often in the treatment versus the control group.

Over the coming years, data will become available on combination therapy of elotuzumab with other drugs in relapsed/refractory but also probably in

induction and maintenance protocols. Of note, combination trials with anti-PD-1 antibodies are ongoing.

10.5 Others

10.5.1 Panobinostat

Panobinostat is an HDAC inhibitor part of another completely different group of drugs that has emerged over the past years in hematology-oncology. The side effects in previously treated patients have been mostly hematological of anemia, neutropenia, lymphopenia, and thrombocytopenia [18].

10.5.2 Immuno-Oncology

After good to excellent results in various solid tumors and lymphomas, early studies are ongoing also in myeloma with PD-1/PDL-1 inhibitors [19]. The occurring side effects were those expected by these drugs and covered elsewhere in this manual. In the coming years, the various combinations of all available drugs with PD-1/PDL-1 inhibitors will be effected and become available. As of now the side effects in immuno-oncology are extensively treated (Chap. 12).

10.6 Summary

Overall, in myeloma, the new agents' imids and proteasome inhibitors have been followed by their second-generation drugs. Thereafter monoclonal antibodies and others have come. As they all have a different profile of side effects, are much easier to administer, more combinations and sequences of drug combinations have become available. The various side effects can be minimized by combining the drugs at appropriate dosages. These increased combinations of drugs make more lines of therapy possible resulting in a remarkably improved survival and quality of life for the patient.

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Dermatologic Side Effects of Systemic Targeted Anticancer Therapy

11

Caroline Robert, Christina Mateus, and Alexander M. M. Eggermont

Abstract

Skin, hair, and nails are almost always modified by systemic cancer therapies. These changes can sometimes result in severe adverse events, but most of the patients present with light and moderate skin side effects. Nevertheless, these dermatologic manifestations can significantly impact patients' quality of life, especially in the case of new targeted agents that are sometimes prescribed continuously over long periods of time.

Patients have to be informed in advance about the skin symptoms that might occur during the course of their treatments. Preventive and symptomatic measures can be advised or prescribed that might optimize treatment compliance and improve quality of life.

Close interaction between oncologists and dermatologist is warranted in order to describe, characterize, and manage the numerous and sometimes new and original skin manifestations of new cancer therapies. In this chapter, we will focus on the side effects associated with targeted anticancer agents since oncologists and physicians are less informed about this field than they are about skin side effects of classical chemotherapeutic agents.

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M. A. Dicato, E. Van Cutsem (eds.), *Side Effects of Medical Cancer Therapy*,
https://doi.org/10.1007/978-3-319-70253-7_11

Keywords
Cancer treatment · Skin adverse events · Targeted agents · Hand-foot skin reaction · Folliculitis · Keratoacanthomas · Skin squamous cell carcinoma · Hair changes paronychia

11.1 Introduction

Abnormalities leading to cell transformation and unrestrained proliferation are usually linked to a deregulation of the normal signaling pathways that control cell differentiation and/or proliferation. New drugs targeting these pathways are being developed. They block more or less specifically one or several enzymes, usually kinases, that are sequentially activated following a chain reaction, from the surface of the cell membrane after binding of a ligand to the corresponding cell surface receptor to the inside of the cell cytoplasm.

Targeted therapies that rely on the specific inhibition of biological events implicated in oncogenic or proliferative processes are now commonly used and still actively being developed. Two types of molecules can be used to inhibit a protein kinase: (1) small molecules designed to inhibit the enzymatic activity of specific kinases (the suffix "–ib" is usually used to name these molecules) and (2) larger molecules, monoclonal antibodies (mAb, suffix "–ab") that bind to ligand or receptors to prevent their interaction and the subsequent pathway activation.

When a skin modification occurs during the course of a cancer treatment, the first question to address is whether this symptom is related to therapy or not. Indeed, infectious, inflammatory, and specific skin lesions as well as graft-versus-host disease-related rash can also be observed in these patients and have to be identified. Sometimes, the patients are treated with multiple drugs, and it is not easy to know which one is responsible for the skin changes observed.

Second, it is critical to identify the serious hypersensitivity skin reactions that require treatment discontinuation and/or specific management. The signs that suggest the possibility of a DRESS (drug reaction with eosinophilia and systemic symptom), Stevens-Johnson syndrome, or a TEN (toxic epidermal necrolysis) include mucosal involvement, bullous lesions, and the association with clinical or biological systemic symptoms such as elevated temperature, transaminase elevation, or hypereosinophilia.

In this chapter, we will review the skin side effects of anti-EGFR agents, anti-vascular endothelial growth factor (anti-VEGFR), anti-kit, platelet-derived growth factor receptor (PDGFR) and bcr-abl inhibitors, RAF inhibitors, as well as the ones induced by mammalian target of rapamycin (mTOR) inhibitors.

Management of these numerous and various side effects associated with targeted agents will also be addressed.

11.2 EGFR Inhibitors

The epidermal growth factor receptor (EGFR) belongs to the family of HER receptors, which comprises four members: HER1 to HER4. HER1/EGFR is expressed by 30–100% of solid tumors, in which increased activity of this receptor is a poor prognostic factor. Several compounds, small molecule inhibitors or monoclonal antibodies, can specifically block HER1 or HER2 or both. All agents targeting EGFR produce the same spectrum of skin side effects with a direct dose effect.

11.2.1 Papulopustular Rash/Folliculitis of the Seborrheic Areas

Papulopustular rash/folliculitis of the seborrheic areas (Fig. 10.1a–c) is the most common, the earliest, and the most impressive skin side effect of anti-EGFR agents,

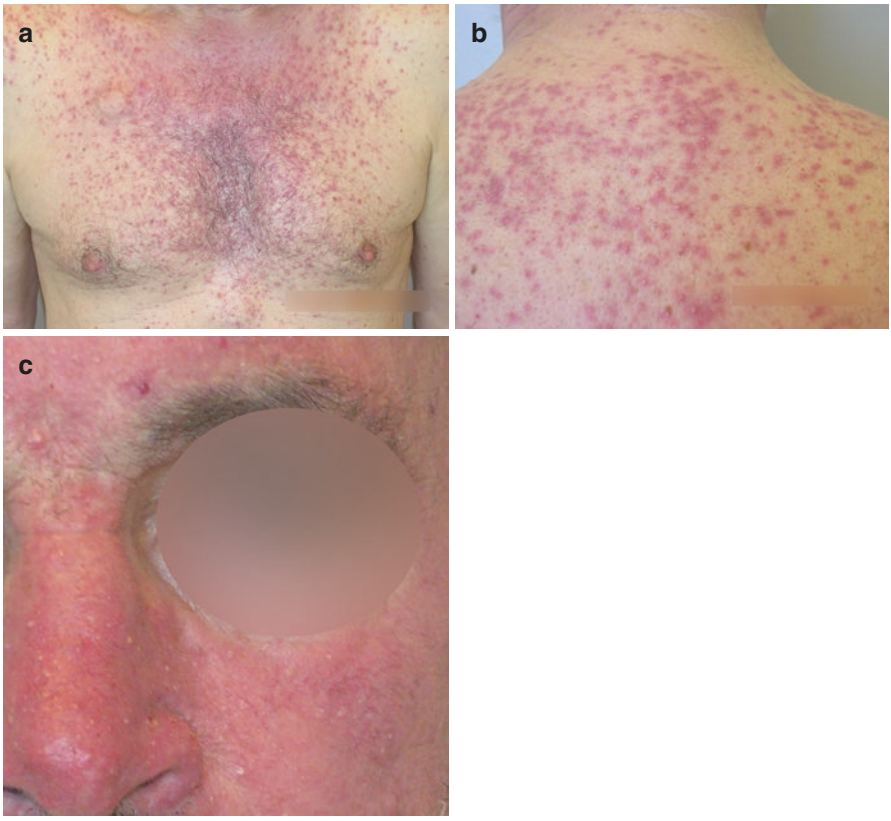

Fig. 10.1 Papulopustular rash in a patient treated with EGFR inhibitor on the seborrheic areas of the trunk (**a**, **b**) and face (**c**)

occurring in more than 75% of patients after 1–2 weeks of therapy [1]. It is often described as acneiform, but in reality it differs from an acne because although the lesions are follicular papulopustules located in the seborrheic areas (face, scalp, trunk), no retentional lesions or comedones are present. The severity varies from a few lesions to a profuse eruption that is described as uncomfortable and sometimes even painful by the patients. Durable pigmented postinflammatory maculae can be observed, especially in patients with pigmented skin. The severity of the rash tends to decrease spontaneously over time and to involve different areas of the body: the limbs can be affected after several months of treatment, whereas the lesions on the face and trunk have disappeared.

Pathology shows nonspecific aseptic suppurative folliculitis, but mononuclear cells are recruited at the early stages, before neutrophils are recruited.

The most commonly used classification is the CTCAE (common terminology criteria for adverse events) grading system version 4. Another classification, more adapted to the side effects of anti-EGFR, has been proposed [2].

Severe rashes (grade 3) occur in less than 10% of patients [1, 3]. They require local and systemic treatment and sometimes a dose reduction and even temporary treatment discontinuation. A progressive attenuation of the folliculitis is usually observed after several months [4].

The mechanism underlying this folliculitis is related to the critical role of the EGF receptor in epidermal and pilosebaceous follicle homeostasis [5, 6] involving primary cytokines like IL-1α (alpha) and TNF-α (alpha) [7].

Interestingly, the occurrence and intensity of this eruption are associated with a better tumor response and overall survival of patients [8]. Several hypotheses can be formulated to explain this correlation. It has been suggested that some polymorphisms of EGFR might be associated with both the appearance of cutaneous signs and better antitumor responses [9]. This toxicity/efficacy correlation could also be explained by better bioavailability of the drug in the skin and the tumor. However, other hypotheses cannot be excluded, such as that of a beneficial effect of the inflammatory/immune reaction in the skin and perhaps also in the tumor.

Management of this eruption relies, as usual, on a good information from the patient prior to treatment initiation as well as on symptomatic topical and/or systemic treatments, depending on the severity of the rash and the impact on the patient [1, 10–13].

Topical treatment, relying on local antibiotics (erythromycin, clindamycin, metronidazole) and copper- and zinc-based antiseptic creams, is usually sufficient in the case of a grade 1 eruption. Patients are allowed and advised to camouflage the lesions with appropriate nonocclusive makeup (tested as noncomedogenic). Topical corticosteroids are usually effective when antibiotics are not sufficient [14].

Systemic treatment is used when the lesions are extensive, profuse, or poorly tolerated by the patient (grades 2 and 3). Cyclines (doxycycline, 100–200 mg/day) are used as first-line therapy for 4–8 weeks and for longer periods of time, if needed. Cyclines are probably active in this indication through their anti-inflammatory action. Preventive treatment with tetracyclines can reduce both the intensity and impact of the eruption, but not the incidence of the rash [15, 16]. Patients should be

advised to avoid sun exposure during tetracycline treatment because of the phototoxicity of this class of antibiotics.

Psychological management of patients should not be neglected, and it is critical to regularly tackle questions about the impact of the eruption on their socio-occupational and emotional lives.

Doses of anti-EGFR should be reduced if the skin reaction is severe or if the treatment is poorly tolerated by the patient (grade 3). The folliculitis is dose dependent and rapidly attenuates after the reduction or interruption of treatment. It does not necessarily recur upon resumption of therapy.

11.2.2 Paronychia

Paronychia (Fig. 10.2) is probably the most concerning side effect of EGFR inhibitors since it frequently has functional consequences and its treatment is difficult. It presents as an inflammation of the periungual folds that resembles an ingrowing nail. In fact, it is a pyogenic granuloma that grows on top of the lateral fold of the nail. It more often affects the toes than the fingers, and more specifically the large toes, probably because it is the most frequently traumatized. Paronychia occurs later in the course of the treatment, after at least a month of treatment, and is less frequently observed than the folliculitis. It occurs in 10–25% of patients [17]. The impact on daily life can be major, as these lesions are painful and can prevent the patient from wearing shoes and interfere with their walking. As with folliculitis, the lesions are aseptic, but superinfections are common. Management is difficult, and the aim is to reduce the extent of the granulation tissue or even destroy it completely by using either topical corticosteroids that can also be injected in the pyogenic

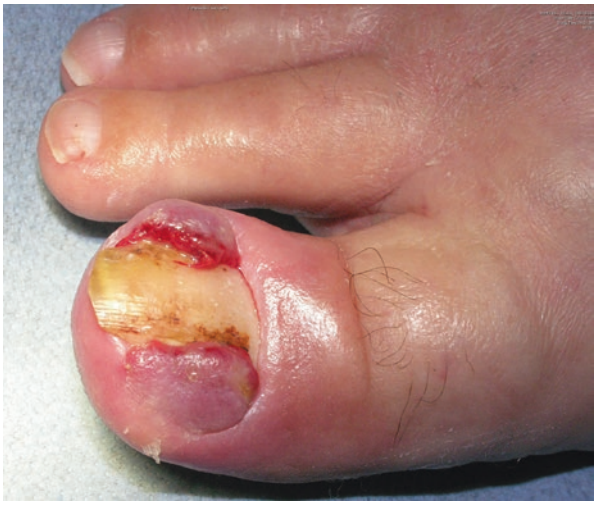

Fig. 10.2 Paronychia of the right big toe in a patient treated with EGFR inhibitor

granuloma (close monitoring is important as steroids promote superinfections) or by chemical cautery with liquid nitrogen, silver nitrate, or trichloroacetic acid. Surgical excision with a partial longitudinal nail plate avulsion including the matrix followed by the application of saturated phenol under local anesthesia can be necessary. It is an effective treatment, but it must be performed by experienced physicians. Indeed, it can induce periostitis if phenol is too vigorously applied. Prophylactic measures such as avoiding friction, traumas, and manipulations and wearing wide, open shoes minimize aggravating factors.

11.2.3 Xerosis

Dry skin is reported in about one-third of the patients after 1–3 months of treatment. It is, in reality, observed in almost all the patients treated with EGFR inhibitors. Xerosis is usually diffuse and easily controlled by emollients. They are more effective if applied after showering, on skin that is still humid. Long, hot baths should be avoided. Xerosis can also predominate on the extremities, where it can result in painful, fissured dermatitis of the finger pulp or heels that can have painful and functional impacts. Vitamin A- or urea-based ointments can help patients.

11.2.4 Hair Modification

Alopecia and a change in hair texture are observed after 2–3 months of treatment in almost all of the patients treated (Fig. 10.3a, b). Alopecia with hair loss in the temporal recesses and the frontal region resembling androgenic alopecia occurs frequently, as does modification of the hair texture, which becomes "straw-like," dry, and fine [1].

Facial hypertrichosis is common, as is eyelash trichomegaly, with fine and wavy eyelashes, after several months of treatment. The eyelashes can curve back toward the conjunctiva and cause keratitis. All these hair side effects are more readily apparent in women, who are inconvenienced more than men by these side effects [18].

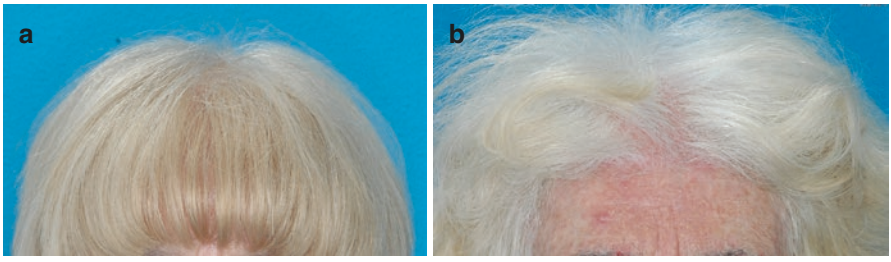

Fig. 10.3 Hair modification. Photo taken before (**a**) and 3 months after (**b**) initiation of treatment with anti-EGFR therapy

Patients can be advised to use hair conditioners, to wax their facial hair, and to regularly trim their eyelashes to prevent conjunctive complications.

11.3 Kit and bcr-abl Inhibitors: Imatinib, Nilotinib, and Dasatinib

Imatinib (Gleevec, Novartis, New York, NY, USA), nilotinib (Tasigna, Novartis, New York, NY, USA), dasatinib (Sprycel, Bristol-Myers Squibb, New York, NY, USA), and bosutinib (Bosulif, Pfizer) inhibit c-kit, PDGFR, and the bcr-abl fusion protein, characteristic for chronic myeloid leukemia (CML). The c-kit receptor (CD117) is activated by mutation in the majority of gastrointestinal stromal tumors (GIST), and the bcr-abl protein is the product of the translocation between chromosomes 9 and 22 found in chronic myeloid leukemia (CML). PDGFRα (alpha) is involved in hypereosinophilic syndrome, and TEL-PDGFRβ (beta) is involved in chronic myelomonocytic leukemia (CMML). The loop, PDGFR/PDGFR, is involved in dermatofibrosarcoma.

Overall, these drugs are well tolerated, and although skin manifestations are the most frequent nonhematologic AEs, they are rarely severe and usually do not require treatment interruption.

More information is available for imatinib than for other, more recent drugs targeting kit or PDGFR. Dermatologic manifestations of imatinib are common but rarely severe, with a prevalence ranging from 9.5 to 69% [19–25].

Edema, predominating on the face and more visible on the periorbital areas in the morning and inferior parts of the body in the evening, is reported in 63–84% of cases and appears, on average, 6 weeks after initiation of treatment [21–26]. It can be severe, with substantial weight gain and even pleural and/or peritoneal effusions or cerebral edema [27]. The pathophysiology is unclear and is thought to be due to a modification of interstitial fluid homeostasis linked to PDGFR inhibition [1].

Maculopapular eruptions are described in up to 50% of the patients and appear, on average, 9 weeks after the initiation of therapy [21, 26]. They are usually mild to moderate, self-limiting, or easily manageable with antihistamines or topical steroids [25]. Pathological studies demonstrate nonspecific perivascular mononuclear cell infiltrates [21, 26]. More severe eruptions (grades 3 and 4) have rarely been reported [21].

Several well-documented cases of Stevens-Johnson syndrome have been published [28–33] as well as several cases of acute generalized exanthematous pustulosis [34, 35] and a case of DRESS (drug reaction with eosinophilia and systemic symptoms) [36].

Nilotinib-associated rash is reported in 17–35% of the patients, pruritus in 13–24%, alopecia in 10%, and xerosis in 13–17%. The majority of the cases are mild to moderate and dose dependent [37, 38].

The most frequently reported dermatologic side effects reported with dasatinib are localized or diffuse maculopapular rashes (13–27%) that are often associated with pruritus (11%) [17].

Exacerbations of psoriasis or psoriasiform eruptions have also been described [21, 39] as well as follicular pustular eruptions similar to pustular psoriasis [39] or eruptions resembling pityriasis rosea [40, 41].

Several cases of palmoplantar hyperkeratoses and nail dystrophies have also been reported [42].

Lichenoid eruptions, sometimes associated with mucosal erosive or lichenoid intrabuccal lesions, have been reported [43–49]. They usually present as red-purple papular lesions localized symmetrically on the trunk and limb.

Pigmentary changes (Fig. 10.4)—localized or diffuse pigmentation modifications—have been frequently reported with imatinib, and rare cases have been reported with dasatinib and nilotinib. Homogeneous depigmentation has been observed, particularly in patients with pigmented black or tanned skin (phototypes 5–6), with a reported prevalence of 16–40% [21, 50, 51]. Conversely, cases of hyperpigmentation or even repigmentation of the skin and hair have been reported [21, 52, 53]. These pigmentary changes are reversible upon treatment discontinuation and might be due to the inhibition of c-kit, whose involvement in melanogenesis via the transcription factor MITF is well established [54, 55].

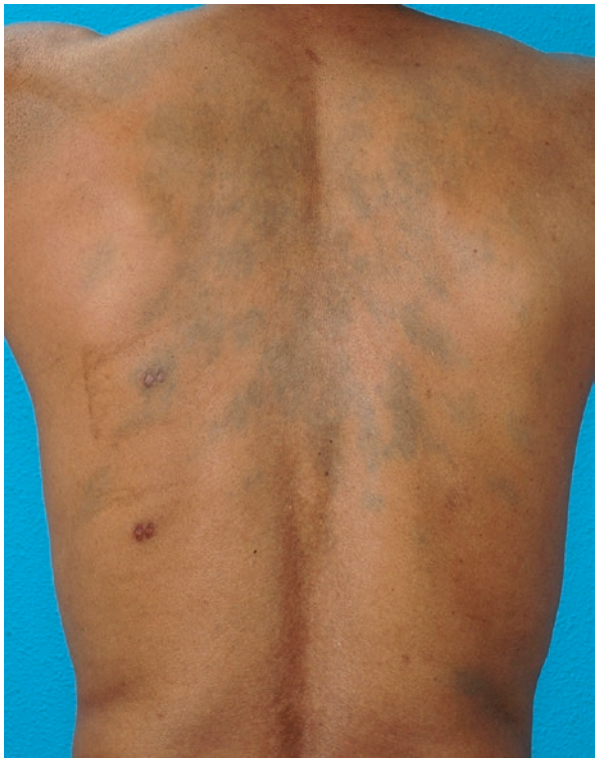

Fig. 10.4 Hyperpigmented maculae in a patient treated with imatinib

Several other various skin manifestations have been reported such as urticaria, neutrophilic dermatosis, vascular purpura [56], pseudolymphoma [57], and photosensitive eruptions [21, 58].

Eruptions and edema seem to be dose dependent. Indeed, the prevalence of drug eruptions increases with the daily dosage [21, 23]. This suggests pharmacologic and not immunologic mechanisms in the development of this type of manifestation [2].

With dasatinib, mucosal involvement has also been reported with mucositis and stomatitis in 16% of the patients [59, 60].

11.3.1 Management

Moderate periorbital edema does not require any treatment. Diffuse and/or severe edema can be alleviated by electrolyte monitoring and diuretics.

The majority of eruptions are easily managed with antihistamines and topical treatments, emollients, and/or corticosteroids and do not require treatment discontinuation. However, since most of the reported side effects are dose dependent, in the case of severe or persistent manifestations uncontrolled by symptomatic treatments, a dose reduction can be done. Obviously, in cases of severe and potentially life-threatening dermatologic adverse effects, treatment should be discontinued and not reintroduced.

11.4 Antiangiogenic Agents: Sorafenib, Sunitinib, and Pazopanib

Small molecule kinase inhibitors like sorafenib (Nexavar, Bayer, Wayne, NJ, USA), sunitinib (Sutent, Pfizer, New York, NY, USA), pazopanib (Votrient, GlaxoSmithKline, Philadelphia, PA, USA), axitinib (Inlyta Pfizer), regorafenib (Bayer), and vandetanib (Caprelsa, AstraZeneca) are antiangiogenic agents targeting VEGF receptors (VEGFR) as well as additional receptors like PDGF receptors, kit, Flt3, and RAF (for sorafenib and regorafenib) and RET (vandetanib). They are indicated in the treatment of renal cell cancer, hepatocellular carcinoma, GIST, or thyroid cancer. Antiangiogenic small molecule inhibitors have various and numerous adverse effects; however, mucocutaneous manifestations are usually the most preeminent of them and frequently impact quality of life of the patients, often threatening compliance to treatment [1, 61, 62]. On the other hand, another antiangiogenic agent, bevacizumab (Avastin, Genentech, South San Francisco, CA, USA), which is a monoclonal antibody binding VEGF and preventing its binding to its receptors, has few cutaneous side effects.

Some adverse effects, like hand-foot skin reaction, genital rash, and subungual splinter hemorrhages, are common to all compounds. Some other manifestations are more specifically observed with one or two of these drugs, as is the case for keratoacanthomas and squamous cell carcinoma of the skin (sorafenib) or photosensitivity (vandetanib).

11.4.1 Hand-Foot Skin Reaction

Hand-foot skin reaction (HFSR) is frequent and usually occurs during the first weeks of treatment. It affects 10–63% of patients treated with sorafenib (with 2–36% of grade 3 severity) [63–69], 10–28% of patients treated with sunitinib (4–12% of grade 3) [70–72], and 11% with pazopanib (2% grade 3) [73–75].

It is different from the hand-foot syndrome seen with classical chemotherapies like capecitabine, 5-fluorouracil (5-FU) (Fig. 10.5), pegylated doxorubicin, or

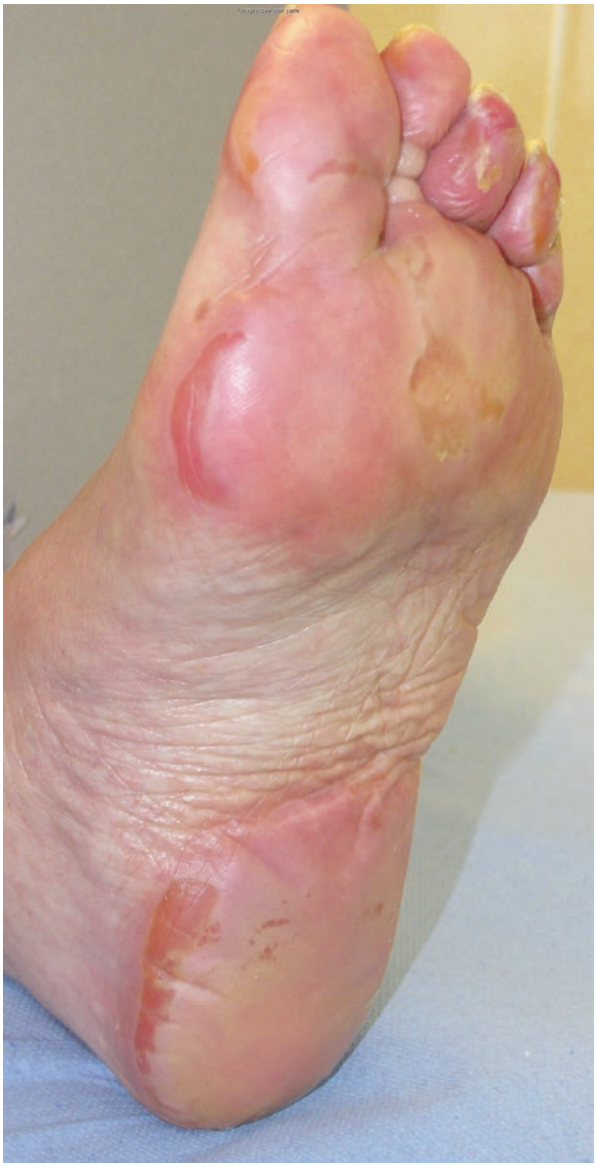

Fig. 10.5 Grade 3 hand-foot skin reaction of a patient treated with 5-fluorouracil

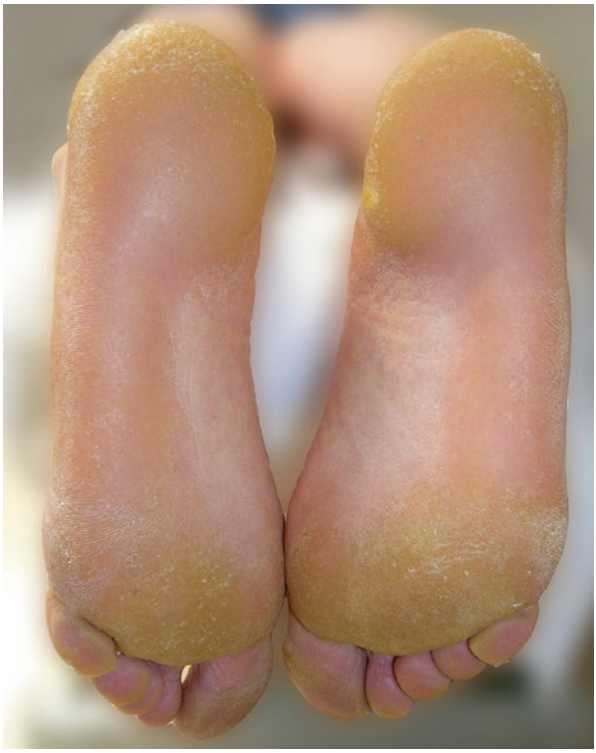

Fig. 10.6 Grade 1 hand-foot skin reaction in a patient treated with sorafenib

cytarabine chemotherapy [76–78]. With VEGFR inhibitors, the lesions are predominantly located on pressure or friction areas (metatarsal heads, heels, sides of the feet, metacarpophalangeal joints) and rapidly become hyperkeratotic (Fig. 10.6). With classical chemotherapies, hand-foot lesions are not limited to pressure areas, and the lesions are inflammatory, erythematous, and possibly desquamative for several weeks. Hyperkeratosis can also occur but later after the beginning of the treatment. Hand and feet inflammation can also be seen with antiangiogenic agents, with erythema, desquamation, and even bullous lesions. An erythematous ring surrounding the hyperkeratotic lesions is also quite common [1, 61, 79]. The HFSR is classically bilateral and symmetrical [80]. Areas of preexisting hyperkeratotic lesions seem to confer a predisposition for painful sole involvement [80, 81]. While not life-threatening, HFSR can be very painful, interfering with everyday activities such as walking or holding objects. Prodromal subjective symptoms with mild tingling and numbness of the hands and feet are frequent [79]. A new quality of life scale has been proposed to grade this adverse event [82].

The main pathological abnormalities observed in HFSR are keratinocyte degeneration with a perivascular lymphocytic infiltrate and sometimes eccrine squamous syringometaplasia [80, 83, 84]. Sequential pathological modifications found during the course of the treatment are changes in the stratum spinosum/

stratum granulosum during the first month and then in the superior layers of the epidermis, in the stratum corneum with hyperkeratosis, and focal parakeratosis after the first month [84].

11.4.1.1 Management

HFSR is clearly dose dependent and may improve with dose reductions or treatment interruptions. Management has not yet been evaluated by controlled studies and is based on prescribers' experience and advice by experts' consensus [85, 86]. Guidance can be split into preventive measures and management strategies.

11.4.1.2 Preventive Measures

The patients must be clearly informed that an HFSR might occur; ideally, they should have their hands and feet examined prior to treatment initiation. A podiatric examination and preventive treatment of preexisting hyperkeratotic areas by mechanical or chemical keratolytic measures (topical 10–50% urea, 2–5% salicylic acid ointments) seem helpful. Emollients can be used to prevent dryness and cracking. Prescription of orthopedic soles may also be helpful in patients with unbalanced sole pressure areas.

Patients should be advised to wear comfortable and flexible shoes and to avoid rubbing and trauma. As a memory aid, these measures can be referred to as the "3C" approach: control calluses, comfort with cushions, and cover with cream [85].

11.4.1.3 Treatment

Treatment is based on symptomatic measures and dose adjustment. Therapeutic measures are proposed according to the three HFSR severity grades NCI-CTCAE classification V4:

Grade 1: Supportive measures include using moisturizing creams, keratolytic agents such as 40% urea, and/or creams or ointments containing 1–10% salicylic acid on the callused areas. Cushioning of the affected regions with gel- or foam-based shock absorber soles and soft shoes is recommended. Treatment is maintained at the same dosage.

Grade 2: The same symptomatic measures as for grade 1 should be initiated promptly; potent topical corticosteroids (clobetasol) can be prescribed on inflammatory lesions for a few days. Analgesic treatment should be considered, if needed. A dose reduction of 50% should be considered until the HFSR returns to grade 0 or 1, particularly in the event of a second episode of grade 2 HFSR. If toxicity resolves to grade 0 or 1, reescalation to the initial dose should be done. Decision whether to reescalate the dose after the second or third occurrence of grade 2 HFSR should be based on clinical judgment and patient preference. If toxicity does not resolve to grade 0 or 1 despite dose reduction, treatment should be interrupted for a minimum of 7 days and until toxicity has resolved to grade 0 or 1. When resuming treatment after dose interruption, treatment should begin at reduced dose. If toxicity is maintained at grade 0 or 1 at reduced dose for a minimum of 7 days, initial dose should be given.

Grade 3: Symptomatic measures as described for grade 2 HFSR should be prescribed as well as antiseptic treatment of blisters and erosions. Treatment should be

interrupted for a minimum of 7 days and until toxicity has resolved to grade 0 or 1. When resuming treatment after dose interruption, treatment should begin at a reduced dose. If toxicity is maintained at grade 0 or 1 at reduced dose for a minimum of 7 days, initial dose should be given again. On the second occurrence of grade 3 HFSR, decision whether to reescalate dose should be based on clinical judgment and patient preference. The same principle applies for the decision whether to discontinue therapy after the third occurrence of grade 3 HFSR.

No systemic therapy has demonstrated any beneficial effect until now.

11.4.2 Subungual Splinter Hemorrhages

Ranging from 3 to 70%, depending on the series, subungual splinter hemorrhages occur with all anti-VEGFR compounds, but their frequency is often underestimated because of their asymptomatic nature. They appear as painless longitudinal black lines beneath the distal part of the nail plate in the first weeks of therapy. They can be clinically identical to those observed in certain systemic diseases such as rheumatoid arthritis, systemic lupus, or Osler's endocarditis, but they are not associated with distant embolic or thrombotic processes, unlike these conditions. Inhibition of the VEGF receptor coupled with local microtraumas could explain the symptom. They disappear progressively at the end of treatment and do not require any treatment [79, 81, 87].

11.4.3 Erythematous Rash

Various erythematous rashes can be observed with all of these compounds—in 13–24% of cases with sunitinib [88, 89], in 10–60% with sorafenib [79, 88, 90], and in 6–8% with pazopanib [73–75]. They usually appear during the first weeks of treatment. They are usually minor, relatively asymptomatic maculopapular eruptions, but can sometimes be more severe and diffuse. They can predominate on the face, as is often the case in the first weeks of sorafenib therapy, where a mild erythematous and desquamative facial rash, resembling seborrheic dermatitis, is frequently observed [79]. Rashes can disappear spontaneously despite continued treatment, but temporary discontinuation of therapy may be necessary in some cases. A case of erythema multiforme has been published [91], and signs of severity such as mucosal involvement, epidermal detachment, and general signs (fever, elevated hepatic enzymes) that can be associated with severe manifestations, toxic epidermal necrolysis, or a DRESS syndrome should always be evaluated.

11.4.4 Hair Modification

Largely underreported in the literature, hair modifications are almost always associated with these drugs. It can be only a minor texture change, with hair usually becoming dryer and curlier. Alopecia occurs in 21–44% of patients on sorafenib

[79, 92]. It occurs slightly less frequently with sunitinib (5–21%) and pazopanib (8–10%) [73–75]. It is usually moderate and develops gradually after several weeks or months. It can be associated with loss of hair in other hairy regions (trunk, arms, pubis).

It is not unusual to see hair growing back even though patients are still on therapy. New-grown hair is usually curlier than it was before treatment.

Reversible hair depigmentation is seen frequently with sunitinib (7–14%) [88, 93, 94] and pazopanib (27–44%) [73, 74]. With sunitinib, which is given 4 weeks on and 2 weeks off, characteristic discoloration can occur, with successive depigmented bands related to periods of treatment and normally pigmented bands associated with periods off treatment [94, 95]. The underlying mechanism of the depigmentation is thought to be a melanogenesis defect resulting from the inhibition of the c-kit pathway; however, this must not be a direct effect of kit inhibition since other kit inhibitors, such as imatinib, dasatinib, or nilotinib, do not induce such systematic hair depigmentation.

11.4.5 Xerosis

The skin becomes dryer with these treatments [1, 79], and symptomatic emollient treatments are usually efficient.

11.4.6 Genital Rash

Genital rash with erythematous, desquamative psoriasiform, or lichenoid lesions can be observed in the genital areas of both male and female patients (Fig. 10.7) [62, 96]. Lesions can involve the vulvar or scrotal areas and extend to the inguinal region. It can occasionally result in phimosis. Histological analysis, when performed, revealed a psoriasiform or lichenoid pattern. Such genital rashes have been observed with sorafenib, sunitinib, and pazopanib [63]. Their real incidence is unknown. Careful and systematic questioning is necessary. Treatment with topical steroid can be proposed after ruling out a bacterial or fungal infection. A temporary dosage modification is sometimes necessary, resulting in a rapid improvement of the symptoms.

11.4.7 Mucositis

Mucositis is characterized by painful inflammation and ulceration of the mucous membranes lining the digestive tracts, whereas stomatitis more specifically refers to inflammation of the mucosae lining the mouth, and cheilitis, to inflammation of the lips. These side effects can give rise to pain and difficulty with speaking or eating. Stomatitis and cheilitis have been reported in 19–35% of sunitinib-treated patients and 19–26% of sorafenib-treated patients [72, 79, 88, 97], usually during the first weeks of treatment. They are dose dependent and can require dose modifications [88].

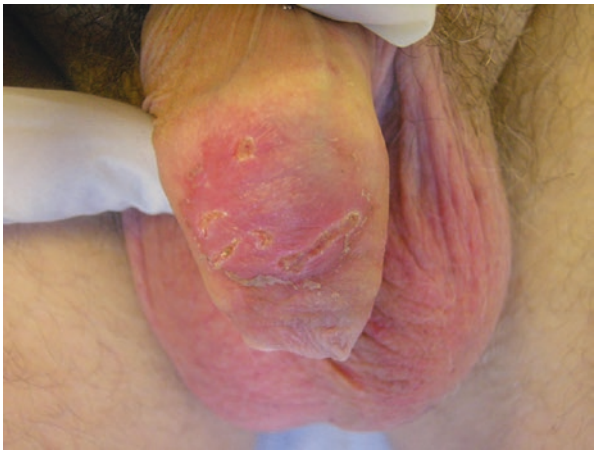

Fig. 10.7 Genital rash in a patient treated with sunitinib

11.4.8 Adverse Effects Specifically Related to Sunitinib

11.4.8.1 Skin Discoloration

A yellow appearance of the skin is seen with sunitinib. It is rapidly reversible and decreases during the 2 weeks off treatment. It is probably due to the bright yellow color of the drug itself [1].

11.4.8.2 Facial Edema

A mild to moderate facial edema is seen in 4.5–24% of patients treated with sunitinib [98]. Hypothyroidism, which is a frequent complication of sunitinib, can exacerbate this edema.

11.4.8.3 Xerostomia

Xerostomia is commonly seen with sunitinib and can result in difficulty with speaking and eating as well as in the occurrence of tooth cavities and vulnerability to mouth infection.

11.4.9 Adverse Effects Related Specifically to Sorafenib

11.4.9.1 Eruptive Nevi

In patients treated with sorafenib, several cases of eruptive nevi have been observed on the face, trunk, or limbs, including the palmoplantar areas [92, 99]. Pathologically, the lesions that were biopsied presented as junctional nevi. Because of the pro-senescence effect of BRAF protein in wild-type BRAF cells [100, 101], it can be hypothesized that these nevi eruption could be linked to an "anti-senescence effect" with the appearance and the development of subclinical preexisting nevi.

11.4.9.2 Squamous Cell Proliferations: Keratoacanthomas and Squamous Cell Carcinomas

Over the last few years, several cases of skin tumors, keratoacanthomas (KA) (Fig. 10.8), and squamous cell carcinomas (SCC) have been described during the course of sorafenib therapy [102, 103]. These lesions could be multiple and occurred several weeks to months after initiating the treatment with an estimated incidence of less than 10%. Beside the contexts of uncommon genetic diseases like Ferguson-Smith or Muir-Torre syndromes, KA is a rare lesion preferentially occurring on sun-exposed areas and presenting as a fast-growing, dome-shaped nodule with a central keratotic crust. It does not give rise to metastases and can occasionally spontaneously regress. Pathologically, it is almost undistinguishable from a well-differentiated SCC, with an exoendophytic proliferation and a crateriform zone of well-differentiated squamous epithelium surrounding a central keratotic plug. The existence of KA is still controversial since for some authors, this entity should be assimilated to a well-differentiated form of SCC [104–106]. In contrast to KA, SCC is a real malignant lesion that does not regress spontaneously and can give rise to metastases. It is a frequent skin tumor and most of the time related to sun exposure or to the existence of precancerous lesions like actinic keratoses, for example. However, the SCC observed during sorafenib therapy do not appear as the typical and most frequently reported SCC. They all exhibit clinical and pathological aspects close to KA and are usually described pathologically as KA-like SCC with nest of atypical cells invading the dermis as well as a crateriform pattern with bulging borders reminiscent of KA. They are not always located on sun-exposed areas [102]. Until now, no metastatic evolution of any SCC induced by sorafenib has been reported, and they rather appear as low-aggressiveness skin tumors.

Looking at the molecules targeted by sorafenib, it could be deduced that this particular side effect was likely to be due to RAF inhibition. Indeed, no KA or SCC has ever been reported with drugs targeting the molecules inhibited by sorafenib in addition to RAF proteins—that is, PDGFR, FLT3, or VEGFR—like sunitinib

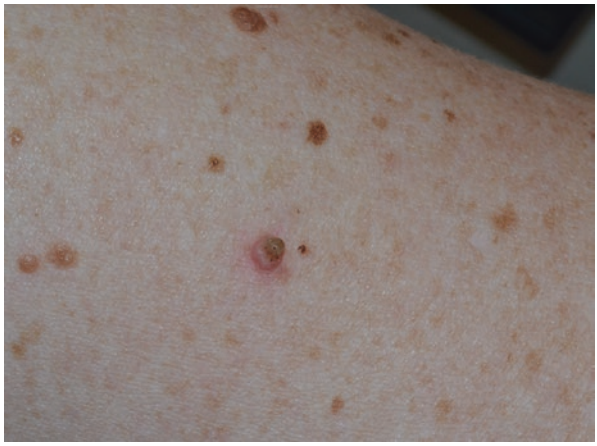

Fig. 10.8 Keratoacanthoma in a patient treated with sorafenib

(VEGFR, KIT, PDGFR, FLT3) or imatinib (kit, PDGFR), for example. This reasoning proved to be correct since similar tumors are now described with the use of two new drugs, presently in development, that efficiently and specifically target RAF proteins and more particularly the mutant form of BRAF: $BRAF^{V600E}$.

BRAF is a serine/threonine kinase, downstream from the RAS proteins and upstream from MEK and ERK on the MAPK (mitogen-activated protein kinase) signaling pathway [107]. This pathway is constitutively activated in several cancers, including melanomas, favoring cell proliferation and survival. It is activated in more than 65% of melanomas resulting from the recurrent $BRAF^{V600E}$ mutation in 40–50% of the cases and NRAS mutation in 15–20% of the cases [108].

The mechanism explaining the appearance of skin tumors with sorafenib and RAF inhibitors is thus due to a paradoxical RAF/MEK/ERK signaling pathway activation via cells that do not harbor the BRAF mutation, especially if the cells have a mutant RAS protein, as was shown in several in vitro models [109–113] and then confirmed with the observations made on patients treated with BRAF inhibitors.

Advice is given that patients' skin should be carefully monitored and that KA and SCC should be removed. These lesions should be completely resected, and simple shaving of the lesions, leading to partial resection only, should not be performed.

In addition to KA and SCC, more or less inflammatory follicular cystic lesions are frequently observed in patients treated with sorafenib: keratosis pilaris [90], microcysts, dystrophic follicular cystic lesions, and perforating folliculitis [79, 90, 102]. Association of these lesions with KA and SCC in the same patients suggests that they could represent various aspects of a wide spectrum of lesions from benign cystic lesions to borderline (KA) and malignant skin tumors (SCC) [102, 112, 113].

With vandetanib, skin photosensitivity is observed in 37% of the patients, and a preventive strict photoprotection is needed. Gray-blue dots or macules, resembling those seen with amiodarone, can also be observed. They usually disappear after treatment discontinuation [86].

11.5 RAF Inhibitors

BRAF is the most frequently mutated protein kinase in human cancer and is the target of several anticancer drugs. The potency and the specificity of BRAF inhibitors available on the market or under clinical development are variable. Sorafenib (Nexavar, Bayer/Onyx) is a pan-RAF inhibitor that also blocks vascular endothelial growth factor receptors (VEGFR)-2, VEGFR-3, platelet-derived growth factor receptor-b (PDGFR-b), fms-like tyrosine kinase 3 (FLT3), and kit. Conversely, vemurafenib (Zelboraf, Roche) and dabrafenib (Tafinlar/Novartis) are highly selective and very potent BRAF inhibitors, effective against tumors harboring BRAF mutations and dependent on the RAF/MEK/ERK pathway, like melanoma with V600E *BRAF* mutation. Both vemurafenib and dabrafenib are specific BRAFV600E inhibitor authorized for the treatment of metastatic melanoma after a rapid clinical

development reporting a rate of objective response around 50% and a benefit in terms of overall survival in this population of patients (Chapman, NEJM; Haushild, Lancet).

However, presently, BRAF inhibitors are not any more used in monotherapy, they are combined with a MEK-inhibitor. Indeed, the combination of BRAF and MEK inhibitors is significantly more effective than the anti-BRAF without inducing more frequent or severe adverse events, although the toxicity associated with the combination is slightly different from the monotherapy [114, 115].

11.5.1 Skin Neoplasms: Papillomas, Keratoacanthomas, Cutaneous Squamous Cell Carcinomas, and Melanomas

In spite of their variability in terms of BRAF selectivity and clinical activity, all RAF inhibitors are associated with one and the same intriguing cutaneous side effect, which is the emergence of borderline squamous cell neoplasms: skin papillomas (Fig. 10.9), keratoacanthomas (KA), and squamous cell carcinomas (SCC).

They occur much more frequently with vemurafenib, having been described in 15–25% of the patients [113, 116] than with dabrafenib [117, 118].

Indeed, vemurafenib frequently induces multiple benign skin tumors resembling human papilloma virus—related papillomas or warts, keratoacanthomas, and cutaneous skin carcinomas during the first weeks or months of treatment. Until now, no metastatic squamous cell carcinoma has been reported, and these skin neoplasms can usually be surgically excised or destroyed.

They are due to a paradoxical activation of the MAPK pathway in keratinocytes associated with BRAF/CRAF heterodimerization and subsequent CRAF activation. Additional somatic events such as a*HRAS* mutation or *EGFR* activation giving rise

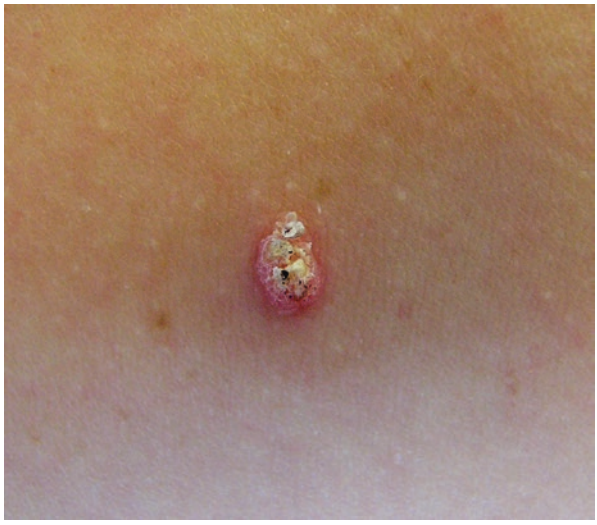

Fig. 10.9 Skin papilloma in a patient treated with vemurafenib

to MAPK pathway coactivation might be required for full transformation of keratinocytes [110–113, 119].

Eruptive nevi and thin melanomas have rarely been reported with vemurafenib [120].

Photosensitivity is frequently observed with vemurafenib in 30–70% of the patients. It can occur with moderate sun exposure, and patients have to observe strict photoprotection measures: clothes and potent sunscreen with UVA and UVB blockers.

Skin rash that can present as maculopapular rash or as a keratosis pilaris occurs frequently, predominantly on the trunk and the extension parts of the limbs. Rashes are reported in up to 75% of the patients but rarely impair treatment continuation.

Hair modification and alopecia similar to the ones that are induced by sorafenib are seen.

Hand-foot skin reaction with hyperkeratosis on pressure and rubbing areas, resembling the symptoms observed with VEGFR inhibitors, is associated with vemurafenib, although the symptoms are less severe than those seen with anti-VEGFR and very few patients present with severe inflammatory or bullous lesions (Fig. 10.10). Hyperkeratosis can also be seen on additional skin-rubbing areas like the nipples or the elbows.

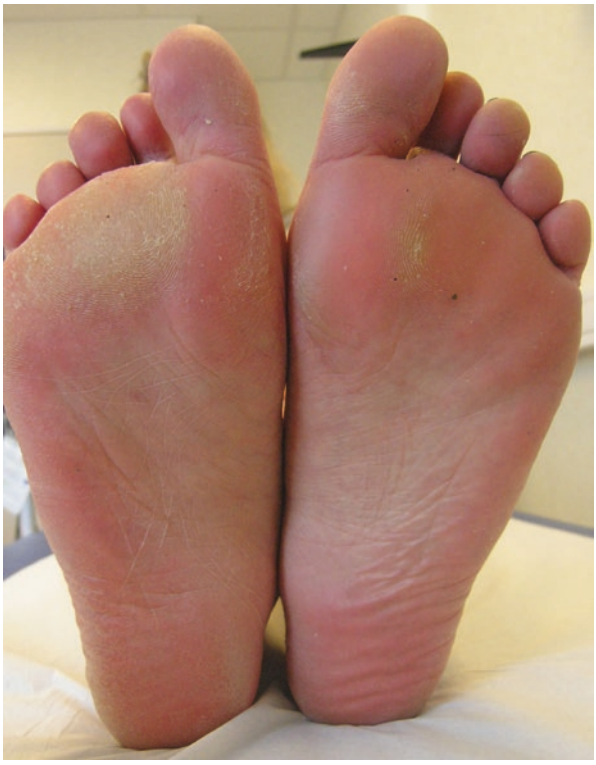

Fig. 10.10 Grade 2 hand-foot skin reaction in a patient treated with vemurafenib

Xerosis is reported in 15–20% of patients and pruritus in 10–30%.

Panniculitis has been reported also with both BRAF inhibitors, as well as skin radiosensitization and radiation recall [121, 122].

11.6 MEK Inhibitors

Two MEK inhibitors are authorized for the treatment of metastatic melanoma in combination with anti-BRAF agents: trametinib (Mekinist, Novartis) combined with dabrafenib and cobimetinib (Cotellic, Roche) in combination with vemurafenib.

Used in monotherapy, MEK inhibitors have a skin toxicity very similar to the one observed with EGFR inhibitors with a papulopustular rash, dry skin, and paronychia [123]. It also can induce edema of the face or of other body parts in some patients.

When used in combination with BRAF inhibitors, these adverse events tend to be less frequent as are those induced by the BRAF inhibitor linked to the paradoxical activation of the MAP-kinase pathway [115, 124].

11.7 mTOR Inhibitors: Everolimus and Temsirolimus

These drugs inhibit the serine/threonine kinase mTOR (mammalian target of rapamycin), inducing downstream dephosphorylation of the mTOR molecular targets and ultimately inhibiting the PI3K/AKT/mTOR signaling pathway. This particular signaling pathway plays a critical role in tumor cell biology, especially in regulating cell growth, survival, and proliferation and apoptosis mechanisms, and is also actively involved in angiogenesis ([116, 120, 125–128] from the previous bibliography).

Two compounds are approved in the treatment of advanced or metastatic renal cell cancer: temsirolimus (Torisel, Wyeth, Madison, NJ, USA) and everolimus (Afinitor, Novartis, New York, NY, USA). These drugs are associated with various side effects, among which mucocutaneous adverse effects are the most frequently represented.

11.7.1 Rash

Skin rash is reported in 25–61% of patients on everolimus and 43–76% of patients on temsirolimus. Usually mild to moderate (0–6% of grade 3 or 4), it appears during the first weeks of treatment. It rarely requires dose modifications or treatment interruption. The rash is not very well characterized, and few series provide details on its clinical presentation. However, the rash is described as papulopustular or acneiform eruptions, in 30–40% of the patients. There are no associated retention lesions

(microcysts, blackheads), which distinguishes this rash from a true acne. A nonspecific neutrophilic dermoepidermal infiltrate has been found pathologically. Therapeutic management is currently, and by analogy, based on that proposed for anti-EGFR inhibitors.

11.7.2 Stomatitis and Oral Ulcerations

Stomatitis, mucositis, cheilitis, and oral ulcerations resembling aphthous ulcers are very common with both drugs: in up to 40% of patients with everolimus and 70% with temsirolimus [129–134]. These side effects are dose dependent and can sometimes entail a dose reduction or treatment interruption, especially in the case of oral ulceration, which is often very painful and can impact patients' food intake.

Xerostomia is reported in 5–11% of patients treated with everolimus, and a dysgeusia has been observed with both compounds [129–134].

Management of these side effects relies on symptomatic measures: topical or systemic analgesics or topical steroids (clobetasol cream of prednisolone mouthwashes). However, these palliative measures are frequently not effective enough, and dose modification, or temporary treatment discontinuation, is often necessary.

11.7.3 Paronychia/Pyogenic Granulomas

Nail involvement, sometimes described as nail dystrophy or thickening of the nail table, has been reported sporadically with both compounds in 5–46% of the cases. Paronychia and/or pyogenic granulomas very similar to the lesions observed with EGFR inhibitors are also observed; their incidence is unknown. Management relies on symptomatic measures similar to the ones proposed for anti-EGFR.

Xerosis and pruritus seem common (20% and 30%, respectively) and are sometimes associated. Pruritus is observed in 40% of patients treated with temsirolimus with 1% of grades 3–4.

Edema is also reported in up to 35% of the patients [98, 129, 134].

11.8 Summary

Systemic cancer treatment, and especially new targeted agents, induces extremely frequent and various skin manifestations that can significantly impact a patient's quality of life and compliance with therapy. Potentially serious adverse events that can require treatment interruption have to be recognized early. Patients must be informed of the risk before the treatments are initiated, and preventive measures can sometimes be advised. Optimal management of these skin side effects requires close interaction between prescribers and dermatologists.

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Immune Checkpoint Inhibition

12

Sarah Sammons, Megan McNamara, April K. S. Salama, and Jeffrey Crawford

Abstract

Immune checkpoint inhibitors (ICI) represent a class of immuno-oncology drugs consisting of monoclonal antibodies occurring against inhibitory receptors or ligands within the immune system including CTLA-4, PD-1, and PD-L1. ICI has transformed oncology in the last decade leading to increased response rates and improved overall survival across several advanced malignancies. ICI is associated with a unique array of toxicities termed immune-related adverse events (IrAEs) which are T-cell-mediated autoimmune toxicities reported in nearly every organ system; most commonly affecting the skin, liver, gastrointestinal tract, and endocrine system. Most IrAEs are manageable with prompt recognition and initiation of appropriate management. General treatment of IrAEs is based on immunosuppression using varying strengths of glucocorticoids. Severe steroid-refractory IrAEs have required nonsteroidal immunosuppressive agents. In this chapter, we describe IrAEs observed with CTLA-4 and PD-1/PDL-1 inhibition by system describing clinical presentation, grading, incidence, time of onset, management, and time to resolution.

Keywords

Immune-related adverse events · Immune checkpoint inhibition · Cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) · Programmed cell death-1 (PD-1) · Side effects · Toxicity · Immunotherapy · Rash · Vitiligo · Pruritus · Diarrhea · Colitis · Hepatitis · Pneumonitis · Hypophysitis · Thyroiditis · Nephritis

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M. A. Dicato, E. Van Cutsem (eds.), *Side Effects of Medical Cancer Therapy*,
https://doi.org/10.1007/978-3-319-70253-7_12

12.1 Immune Checkpoint Inhibition

In the past 10 years, immune checkpoint inhibition (ICI) has transformed the management of advanced cancer. Checkpoint inhibitors represent a class of drugs consisting of monoclonal antibodies (mAbs) against naturally occurring inhibitory receptors within the immune system, called "immune checkpoints." In healthy individuals, these immune checkpoints function to downregulate the immune response, prevent autoimmunity, and limit damage to normal tissue following activation of the immune response. Immune checkpoints are also up-regulated in several tumors and are involved in tumor escape mechanisms from immune surveillance. By blocking an inhibitory pathway, treatment with immune checkpoint inhibitors unleashes the immune response and has been shown to have an antitumor effect in several malignancies [1].

Inhibitors of CTLA-4, PD-1, and programmed cell death ligand-1 (PD-L1) immune checkpoints are currently commercially available or under clinical investigation across multiple malignancies. Ipilimumab, a CTLA-4 inhibitor, became the first ICI to achieve Federal Drug Administration (FDA) approval in 2011, when it was approved for metastatic melanoma on the basis of improved survival in a phase III clinical trial [2]. Its label has since been expanded to include the use of adjuvant treatment for patients with stage III melanoma [3]. Ipilimumab has been studied at different doses and schedules, and its toxicity is dose dependent [4]. The PD-1 inhibitor pembrolizumab is also FDA approved for advanced melanoma [5] as well as metastatic non-small cell lung carcinoma (NSCLC) [6] both second line [7] and first line [8] based on phase III trials showing survival benefit in both of those settings. FDA approval has also been granted for pembrolizumab in squamous cell carcinoma of the head and neck (SCCHN) after progression on platinum-based chemotherapy, refractory classical Hodgkin's lymphoma treated with greater than three lines of therapy [9], metastatic urothelial carcinoma not eligible for or after progression on cisplatin-based chemotherapy [10], and microsatellite instability-high (MSI-H) solid tumors with no alternative options [11]. Another PD-1 inhibitor nivolumab is FDA approved for metastatic NSCLC [12, 13], metastatic renal cell carcinoma (RCC) [14], and squamous cell carcinoma of the head and neck (SCCHN) [13], based on improved survival in phase III trials. Nivolumab was also recently granted accelerated approval in the treatment of relapsed refractory Hodgkin's lymphoma and metastatic urothelial carcinoma that is platinum refractory based on the results of phase II trials [15, 16]. The PD-L1 inhibitor atezolizumab is approved for cisplatin-ineligible metastatic urothelial carcinoma [17], as well as NSCLC [18]. Durvalumab and avelumab both recently received accelerated approval for platinum refractory advanced or metastatic urothelial carcinoma [19, 20]. In addition to these FDA-approved indications, PD-1and PD-L1 inhibitors have shown activity in several tumor types [11, 17, 21, 22], and more regulatory approvals are anticipated. Multiple mAbs against PD-1 and programmed cell death ligand-1 (PD-L1) are under development, expanded regulatory approval of these agents and others are anticipated in Europe and globally, and our understanding of the biology of these agents continues to rapidly grow. This chapter will discuss ICIs that have passed

regulatory approval and are commercially available for oncologic practice outside of clinical trials shown in Table 12.1.

ICI clinical trials have generally excluded patients with underlying autoimmune disease, a medical condition requiring systemic treatment with corticosteroids or other immunosuppressive medication, hepatitis B or C, or a history of HIV. However, a number of retrospective case series have suggested that ICI is possible in patients with underlying autoimmune disorders or hepatitis. The use can be associated with exacerbations of autoimmune disease, and it is important to weigh the risks and benefits of therapy on an individual patient basis [23].

12.2 Immune-Related Adverse Events: Overview

The benefits of ICI are numerous, including increased response rates and improved overall survival in several malignancies. The price for these benefits is a new toxicity profile that is distinct from the side effects of cytotoxic chemotherapy and other targeted agents. ICI is associated with a unique array of toxicities termed immune-related adverse events (irAEs). IrAEs are T-cell-mediated autoimmune toxicities reported in every organ system but most commonly affecting the skin, liver, gastrointestinal tract, and endocrine system. Histopathological analysis of affected organs usually reveals T-cell-rich lymphocytic and neutrophilic infiltration. IrAEs are theorized to be caused by immune recognition and activation against self-antigens that would normally be dampened by intact immune surveillance.

The overall incidence of all-grade and high-grade irAEs with CTLA-4 checkpoint blockade is 72% and 24%, respectively, with death occurring in less than 1% of patients [4]. IrAEs associated with CTLA-4 inhibition most commonly occur in the dermatologic (44%), gastrointestinal (35%), hepatic (5%), and endocrine (6%) systems. Other rare events have included neurologic, hematologic, ophthalmologic, or rheumatologic diseases [4].

Compared to treatment with CTLA-4 mAbs, PD-1/PD-L1 inhibition results in less frequent and less severe irAEs. There is a lack of standardization of reporting irAEs across trials making cumulative incidence reporting difficult. All-grade toxicity, both immune and nonimmune, for anti-PD-1 mAbs occurs in 58–79% of patients with high-grade toxicity observed in 7–19% [13, 14, 24]. A pooled safety analysis of nivolumab in 4 phase I–III clinical trials including 576 patients with advanced melanoma found grade 3–4 irAEs in 4% of patients with no drug-related deaths [25]. Most common irAEs included the skin (34%), GI tract (13%), endocrine glands (8%), and liver (4%).

Combination of ipilimumab and nivolumab therapy has a higher incidence and severity of irAEs than either agent alone. This increased toxicity was demonstrated in a phase III study assessing combined nivolumab and ipilimumab or monotherapy in untreated metastatic melanoma leading to grade 3 or 4 toxicity in more than half of patients [26]. An analysis of the expanded access program for ipilimumab and nivolumab at one institution reported that nearly half of all patients were hospitalized at least once during a course of therapy, most commonly related to severe irAEs [25].

Table 12.1 FDA-approved immune checkpoint inhibitors

Drug	Target	Antibody	Approval	Indication
Ipilimumab (YERVOY®)	CTLA-4	IgG1	2011 metastatic melanoma 2015 Adjuvant[a]	– Unresectable/metastatic melanoma – Adjuvant treatment of melanoma with regional lymph node involvement, following complete resection
Nivolumab (OPDIVO®)	PD-1	IgG4	2014 Melanoma 2015 NSCLC, RCC 2016 HL SCCHN 2017 Urothelial carcinoma	– Unresectable or metastatic melanoma (BRAF V600 WT and mutation-positive) – Metastatic non-small cell lung cancer – (NSCLC) with progression on/after platinum-based chemotherapy – Advanced renal cell carcinoma (RCC) who have received prior antiangiogenic therapy – Classical Hodgkin's lymphoma (HL) that has relapsed or progressed after autologous hematopoietic stem cell transplantation (HSCT) and posttransplantation brentuximab vedotin – Recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN) with progression on/after platinum-based chemotherapy – Locally advanced or metastatic urothelial carcinoma with disease progression during or following platinum-based chemotherapy or within 12 months of neoadjuvant/adjuvant treatment with platinum-based chemotherapy

Table 12.1 (continued)

Pembrolizumab (KEYTRUDA®)	PD-1	IgG4	2014 Melanoma 2015 NSCLC 2016 SCCHN NSCLC 2017 HL Urothelial carcinoma MSI-H tumors	– Unresectable or metastatic melanoma – Metastatic (advanced) PD-L1+ NSCLC with progression on/after platinum-based chemotherapy – Initial treatment for metastatic NSCLC whose tumors express PDL-1 >50% – Initial treatment metastatic non-squamous NSCLC in combination with pemetrexed and carboplatin – (SCCHN) with progression on/after platinum-based chemotherapy – Refractory HL ≥3 lines of therapy – Metastatic urothelial carcinoma not eligible for cisplatin chemotherapy – Locally advanced or metastatic urothelial carcinoma with disease progression during or following platinum-based chemotherapy or within 12 months of neoadjuvant/adjuvant treatment with platinum-based chemotherapy microsatellite instability-high (MSI-H) solid tumors with no alternative options – MSI-H colon cancer after fluoropyrimidine, oxaliplatin, and irinotecan
Atezolizumab (Tecentriq®)	PD-L1	IgG1	2016 Urothelial carcinoma NSCLC	– Locally advanced or metastatic urothelial carcinoma with disease progression during or following platinum-based chemotherapy or within 12 months of neoadjuvant/adjuvant treatment with platinum-based chemotherapy – Metastatic urothelial carcinoma not eligible for cisplatin chemotherapy – Metastatic NSCLC with progression on/after platinum-based chemotherapy
Durvalumab (Imfinzi®)	PD-L1	IgG1	2017 Urothelial	– Locally advanced or metastatic urothelial carcinoma with disease progression during or following platinum-based chemotherapy or within 12 months of neoadjuvant/adjuvant treatment with platinum-based chemotherapy
Avelumab (Bavencio®)	PD-L1	IgG1	2017 MCC Urothelial	– Metastatic Merkel cell carcinoma (MCC) – Locally advanced metastatic urothelial carcinoma progressed on platinum-based agent

[a]Ipilimumab is given at 10 mg/kg in the adjuvant setting

The Common Terminology Criteria for Adverse Events (CTCAE) is a set of standardized definitions for adverse events published by the National Cancer Institute. It consists of a grading severity score from 1 to 5 with associated descriptive terminology. These criteria are widely accessible and can be found at http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf [27]. More specific irAE grading systems have been proposed but not yet adopted. There is marked heterogeneity in irAE reporting across trials and a need for standardization.

Patient reporting and physician recognition are encouraged as soon as possible because outcomes in irAE treatment are time sensitive. IrAEs are manageable with prompt recognition and initiation of appropriate management usually resulting in reversibility. General treatment of irAEs is based on immunosuppression using varying strengths of glucocorticoids. More severe grade irAEs that are steroid refractory have required nonsteroidal immunosuppressive agents. Surgical intervention for severe colitis leading to perforation has also been required. Fatigue, nausea, asthenia, pyrexia, and infusion reactions are common side effects of ICI. The management of these side effects is supportive and will not be discussed.

In this chapter, we describe irAEs observed with mAbs targeting CTLA-4 and PD-1/PDL-1 by system describing clinical presentation, grading, incidence, time of onset, management, and time to resolution. ICI is a new and rapidly evolving therapeutic class; therefore, its toxicity profile, incidence, and management are continually under investigation and ongoing.

12.3 Cutaneous Toxicity

12.3.1 Clinical Presentation

Cutaneous toxicities are common irAEs for both CTLA-4 and PD-1 inhibition including rash (maculopapular, lichenoid, eczema, etc.), vitiligo-like skin hypopigmentation, and pruritus. Severe and life-threatening cutaneous toxicity such as Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis are rare but have occurred.

12.3.1.1 Rash

Several diverse presentations of rash can manifest including maculopapular, lichenoid, eczema, Sweet's syndrome, urticarial dermatitis, bullous pemphigoid, TENS, and SJS. The rash most commonly observed with ICI is similar to drug rash seen in commonly used medications such as antibiotics, nonsteroidal anti-inflammatory drugs [28]. This entity is described as discrete, erythematous, pruritic papules coalescing into thin plaques. The rash most often involves the trunk and extremities; sparing the face, head, palms, and soles. These lesions can be pruritic but are not always. Histologically, biopsy of these lesions has shown perivascular immune cell infiltrates in superficial dermis extending to the epidermis with lymphoid aggregates composed of a mixture of $CD4^+$ and $CD8^+$ T cells [29]. Figure 12.1 demonstrates a typical maculopapular rash seen with ipilimumab therapy for advanced melanoma.

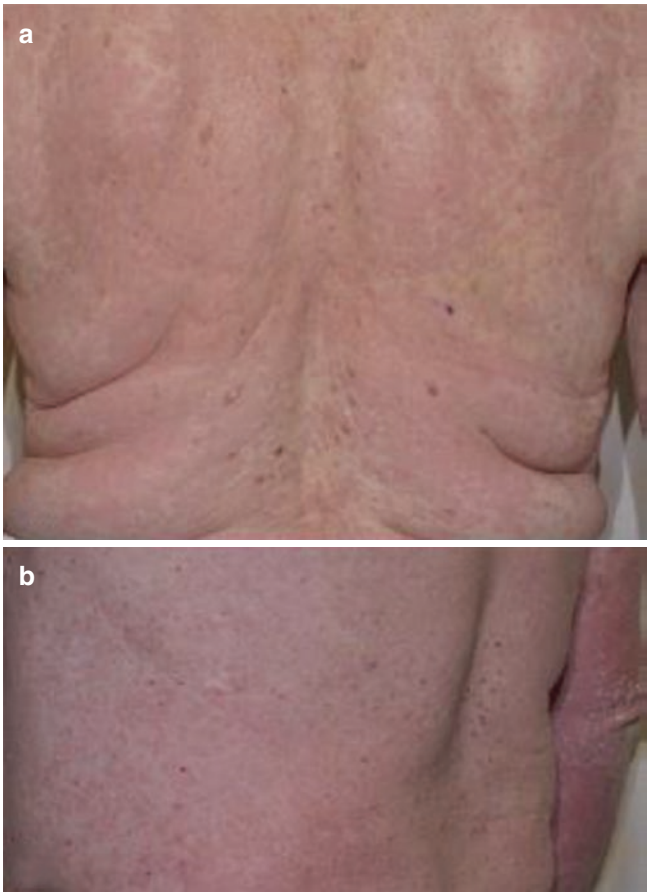

Fig. 12.1 Two cases of rash related to ipilimumab in patients with metastatic melanoma. (**a**) Generalized erythema, erythematous macules, and papules. (**b**) Generalized erythema, erythematous macules, erythematous and some heme-crusted papules, and exfoliative scale on upper extremities. Adapted from Kira Minkis, Benjamin C. Garden, Shenhong Wu, Melissa P. Pulitzer, Mario E. Lacouture. The risk of rash associated with ipilimumab in patients with cancer: A systematic review of the literature and meta-analysis. Journal of the American Academy of Dermatology, Volume 69, Issue 3, 2013, e121–e128

Lichenoid reactions have been described in several patients receiving anti-PD-1 mAbs [30]. These lesions are characterized as multiple discrete, erythematous, violaceous, papules, or plaques mainly on the chest or back sparing mucous membranes. Figure 12.2 demonstrates three cases of lichenoid reactions manifesting after ICI.

Biopsy revealed lichenoid interface dermatitis with occasional eosinophils and scattered apoptotic basal keratinocytes consistent with a lichenoid drug reaction. CD3-positive infiltrate with approximately 10% of the T cells staining positive for PD-1 [31].

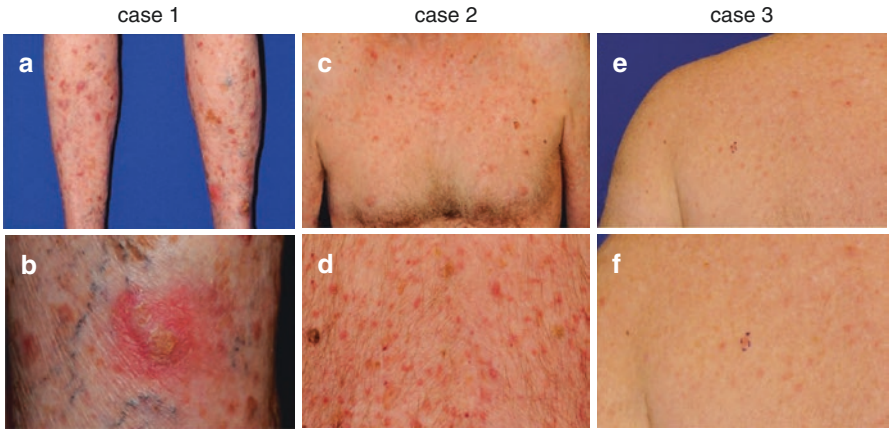

Fig. 12.2 Three cases of cutaneous lichenoid drug eruption from PD-L1 inhibition. Case 1: (**a**) erythematous to violaceous eruption of hyperkeratotic papules and plaques on the legs of case 1. (**b**) Close-up view of lesion on upper extremity. Case 2: (**c**) discrete, erythematous, edematous papules and plaques with minimal scaling of the torso and extremities with sparing of the face. (**d**) Close-up view of lesions on lower back. Case 3: (**e**) papular eruption with monomorphic, flat-topped, faintly erythematous papules and plaques with fine scale distributed over his chest, back, and abdomen. (**f**) Close-up view of lesions on shoulder. Adapted from Ref. [31]

Severe, life-threatening rashes are rarely seen in ICI. Bullous pemphigoid has been described in anti-PD-1 mAb treatment [30, 32]. Toxic epidermal necrolysis has been seen with anti-CTLA-4 and anti-PD-1 mAbs [2, 33]. Any rash complicated by full-thickness dermal ulceration, necrosis, bullous, or hemorrhagic manifestations should be considered severe and treated accordingly.

12.3.1.2 Skin Hypopigmentation/Vitiligo

Vitiligo-like depigmentation is a harmless autoimmune toxicity that can be esthetically distressing to patients. Vitiligo presents as the presence of pale, patchy areas of depigmented skin. The hypopigmentation results from strong anti-melanocyte immunity that also targets healthy melanocytes in the case of advanced melanoma treated with anti-CTLA-4 and anti-PD-1 mAbs [34]. The cumulative incidence of vitiligo was 2.0% in a large meta-analysis of patients with stage III–IV melanoma receiving immunotherapy including CTLA-4 blockade or anti-PD-1 mAbs [34]. However, vitiligo has been seen in up to 10% of melanoma patients treated with anti-PD-1 mAbs [24].

Development of vitiligo is associated with significant progression-free survival and overall survival in advanced melanoma, which can be encouraging to both the patient and physician [34]. Vitiligo occurs often in melanoma patients treated with ICI but is less frequently reported in other malignancies including NSCLC and RCC clinical trials.

12.3.1.3 Pruritus

Development of pruritus with ICI is relatively common with or without associated rash. Pruritus is an unpleasant skin sensation that provokes scratching that can lead to self-inflicted skin changes such as edema, papulation, excoriations, and lichenification. This sensation can be very distressing to patients and can markedly impact quality of life.

12.3.2 Grading

The CTCAE (version 4.03 published June 14, 2010) for rash maculopapular, vitiligo, and pruritus is below. Rash grading is based on body surface area (BSA) involvement and quality of life. Surface area quantification can be difficult to calculate, and the Lund and Browder chart shown below in Fig. 12.3 can be used for accurate quantification [35]. Any skin toxicity that is life-threatening is considered grade 4. Any skin toxicity leading to death is considered grade 5.

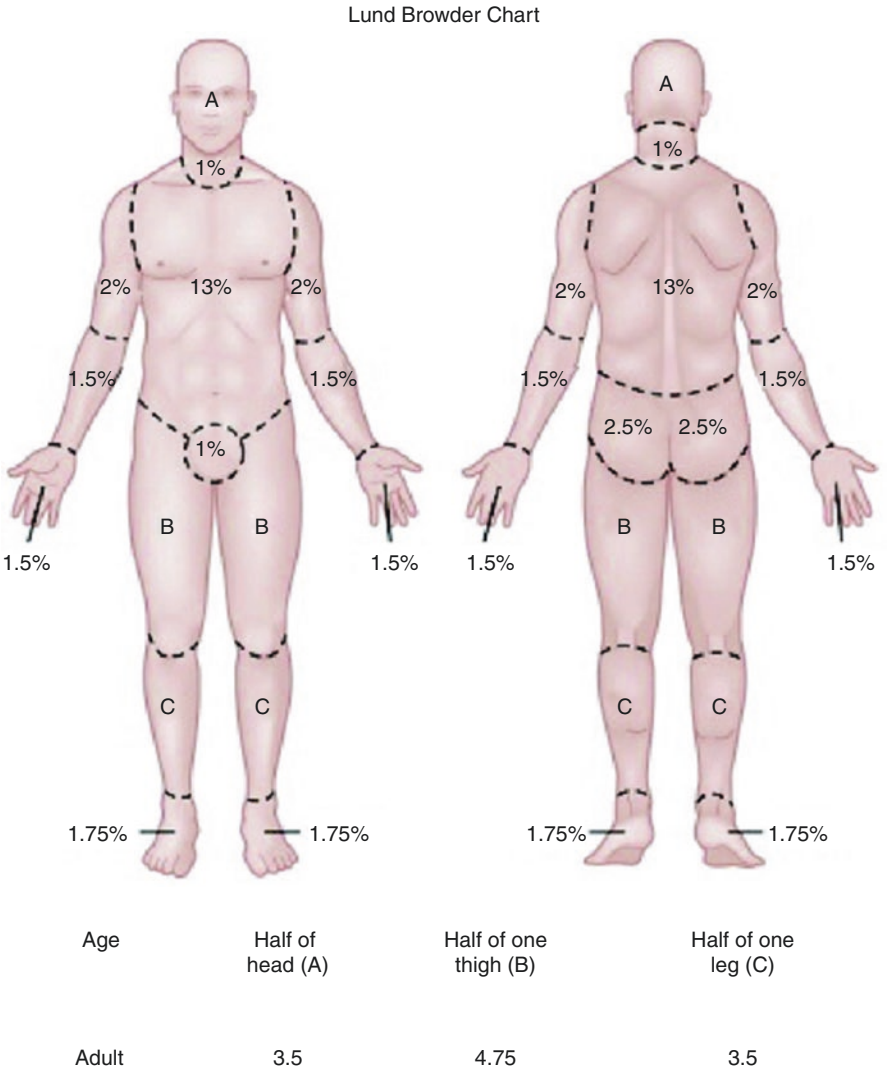

Fig. 12.3 Lund and Browder chart for estimating body surface area involving rash which can be used to quantitate rash severity from immune checkpoint inhibition. Adapted from Marx J, Hockberger R, Walls R. Rosen's Emergency Medicine. 7th ed. Philadelphia, PA: Mosby Elsevier; 2009. p. 760

Rash maculopapular:

Grade 1: Macules/papules covering <10% BSA with or without symptoms (pruritus, burning, tightness)
Grade 2: Macules/papules covering 10–30% BSA with or without symptoms (pruritus, burning, tightness); limiting instrumental ADL
Grade 3: Macules/papules covering >30% BSA with or without symptoms (pruritus, burning, tightness); limiting self-care ADL

Skin hypopigmentation (vitiligo):

Grade 1: Hypopigmentation or depigmentation covering <10% BSA; no psychosocial impact
Grade 2: Hypopigmentation or depigmentation covering >10% BSA; no psychosocial impact

Pruritus:

Grade 1: Mild or localized; topical intervention indicated
Grade 2: Intense or widespread; intermittent; skin changes from scratching (edema, papulation, excoriations, lichenification, oozing/crusts); oral intervention indicated; limiting instrumental ADL
Grade 3: Intense or widespread; constant; limiting self-care ADL or sleep; oral corticosteroid or immunosuppressive therapy indicated

12.3.3 Incidence

The incidence and severity of dermatologic irAEs vary in different tumor types with the highest rates of skin toxicity occurring in melanoma. Cutaneous irAEs of all grades occur in approximately 40% of patients treated with PD-1 inhibition and between 40 and 50% treated with CTL-4 inhibition in advanced melanoma [4, 30, 36, 37]. Severe (grade 3 or 4) cutaneous reactions are rare occurring in <2% of patients with anti-CTLA-4 mAbs and <1% with anti-PD-1 mAbs.

A recent meta-analysis performed including 1265 melanoma patients from 22 clinical trials treated with anti-CTLA-4 mAbs found all-grade skin toxicity in 44% of patients and high-grade toxicity in 1.4% [4]. A recent pooled safety analysis of four clinical trials of BRAF wild-type melanoma patients treated with nivolumab found the following cutaneous toxicities: pruritus (16.5%), rash (12%), vitiligo (5.4%), and maculopapular rash (5.4%) [38].

All dermatologic toxicity occurs less frequently in the treatment of other solid tumors such as NSCLC and renal carcinoma. The use of pembrolizumab in 495 patients with advanced NSCLC led to grade 1 or 2 cutaneous toxicity in only 10% of patients with only 1 patient developing grade 3 or 4 cutaneous toxicity [6].

Rare cases of severe rash including Stevens-Johnson syndrome, bullous pemphigoid, and toxic epidermal necrolysis are reported in <1% of patients [2, 32, 33].

12.3.4 Time of Onset

Skin toxicity is usually the earliest irAE to occur. Median time to onset of moderate, severe, or life-threatening immune-mediated rash is 3 weeks and ranged up to 4.0 months with ipilimumab [39, 40]. The median time to onset of cutaneous toxicity with nivolumab therapy was 5 weeks in a pooled safety analysis [25].

12.3.5 Management

Algorithms have been developed to aid in the treatment of skin toxicity and are recommended [35, 41]. Providers should encourage the use of moisturizers, limited sun exposure, and UV protection. Grade 1 toxicity can be treated for symptomatic relief with topical corticosteroid ointments, oral antihistamines such as diphenhydramine or hydroxyzine, and moisturizing lotions. Serum liver and renal function tests should be performed. Grade 1 cutaneous toxicity does not require interruption in of ICI.

For grade 2 skin toxicity, symptomatic relief as well as topical corticosteroids can be used initially. Systemic corticosteroids should be considered at 0.5 mg/kg/day prednisone or equivalent if there is no improvement in symptoms within 1 week. Experienced practitioners recommend continuation of ICI if patients are asymptomatic and have involvement of <30% of body surface area or toxicity can be managed with topical corticosteroid creams and antihistamines. For patients with 10–30% of body surface area involvement that is symptomatic, ICI should be held, and steroids at 0.5–1 mg/kg prednisone or equivalent should be administered for control of symptoms. Dermatologic evaluation and biopsy should be considered.

For grade 3 skin toxicity, ICI should be held. Patients should be given symptom management and 1–2 mg/kg prednisone or equivalent daily to control symptoms. Dermatologic consultation is recommended. Therapy can be reinitiated after resolution of symptoms or improvement to grade 1 toxicity, and steroids have been tapered to less than 10 mg of prednisone daily.

Development of grade 4 (life-threatening) skin toxicity including SJS or TEN requires admission to the hospital for supportive care including intravenous corticosteroids, intravenous fluids, consideration of antibiotics, pain management, and a formal dermatology consultation. ICI should be discontinued permanently for rashes that show signs of blistering, dermal ulceration, necrosis, bullous, or hemorrhagic changes. Systemic corticosteroids initiated at 1–2 mg/kg/day prednisone or equivalent should be administered and tapered over at least 1 month.

Cessation of drug is not usually recommended for vitiligo. There are dermatologic treatments for vitiligo including immunosuppression, UV therapy, and depigmentation therapy; however, this toxicity is cosmetic in the setting of life-threatening

malignancy. Vitiligo is permanent, and referral to dermatologist is warranted if depigmentation causes the patient significant emotional distress.

Lichenoid reactions do not require cessation of drug in general. Treatment including topical steroids such as triamcinolone can be used in symptomatic cases and have improved pruritus and rash. In a series of three patients treated with anti-PD-1 mAbs developing lichenoid reactions, two patients continued therapy without any intervention and rash remained mild [31].

Studies have shown that development of cutaneous irAEs, specifically vitiligo-like depigmentation, may be of positive prognostic value. In a meta-analysis of 27 studies, vitiligo development was significantly associated with both improved progression-free survival ($p < 0.005$) and overall survival ($p < 0.003$) [34]. Retrospective analyses showed that patients who developed any cutaneous irAEs, not limited to vitiligo, while treated with pembrolizumab for advanced melanoma or NSCLC had significantly longer progression-free intervals [36].

12.3.6 Time to Resolution

In phase III clinical trials, ipilimumab-mediated moderate rash was treated with systemic steroids for a median of 15 days. Patients with severe rash were treated with systemic steroids for a median of 21 days with a time to resolution ranging up to 3.6–4.3 months [39]. In nivolumab-mediated rash, median time to resolution in a pooled safety analysis was 29 weeks [25]. Most patients have resolution of rash, and only a minority of patients experienced rash upon reinitiating drug.

12.4 Gastrointestinal Toxicity

12.4.1 Clinical Presentation

Diarrhea and enterocolitis are well-described toxicities of ICI. Patients will report loose, watery stools several times daily, depending on severity. Frequency of diarrhea should be assessed carefully. Stool containing blood or mucous is concerning for colitis. Physicians should inquire about the presence of abdominal pain, fever, nausea, or vomiting, as these symptoms are concerning for colitis, impending ileus/obstruction, or perforation. Physical exam should be performed specifically looking for abdominal tenderness or peritoneal signs. In the case of severe abdominal pain, stat imaging should be obtained to rule out ileus, colitis, or abdominal perforation.

The most common computed tomography (CT) findings of ipilimumab-mediated colitis are mesenteric vessel engorgement and bowel wall thickening, followed by fluid-filled colonic distention in either diffuse or segmental patterns [42]. Gastrointestinal consultation is recommended in the case of prolonged grade 2 or grade 3/4 diarrhea or colitis in order to obtain flexible

sigmoidoscopy or colonoscopy, which can aid in the diagnosis of immune-mediated colitis. On endoscopy in patients with immune-mediated enterocolitis, gross ulceration or erythema is typically observed, and three histologic patterns have been described: neutrophilic inflammation only (46%), lymphocytic inflammation only (15%), or combined neutrophilic and lymphocytic inflammation (38%) [43].

12.4.2 Grading

Diarrhea:

Grade 1: Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline
Grade 2: Increase of 4–6 stools per day over baseline; moderate increase in ostomy output compared to baseline
Grade 3: Increase of >7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self-care ADL
Grade 4: Life-threatening consequences; urgent intervention indicated
Grade 5: Death

Enterocolitis:

Grade 1: Asymptomatic; clinical or diagnostic observations only; intervention not indicated
Grade 2: Abdominal pain; mucus or blood in stool
Grade 3: Severe or persistent abdominal pain; fever; ileus, peritoneal signs
Grade 4: Life-threatening consequences; urgent intervention indicated
Grade 5: Death

12.4.3 Incidence

Diarrhea and enterocolitis are common gastrointestinal (GI) irAEs associated with ICI with a higher incidence in patients treated with anti-CTLA-4 mAbs, compared to PD-1/PDL-1inhibition. Approximately 1/3 of patients treated with CTLA-4 checkpoint blockade will develop diarrhea and/or colitis of any grade, and up to 11% will develop severe grade 3 or 4 toxicity [4]. In contrast, approximately 8–19% of patients treated with anti-PD-1 mAbs developed diarrhea and/or colitis of any grade with severe GI toxicity occurring in only 1% [6, 14, 24, 26]. Concurrent use of anti-CTLA-4 and anti-PD-1 mAbs leads to GI toxicity in up to 44% of patients with severe GI toxicity in 9.3% of patients [26].

12.4.4 Time to Presentation

Across several clinical trials, ipilimumab-mediated enterocolitis presents at a median of 6.3 weeks for grade 2 enterocolitis and 7.4 weeks for grade 3–5 enterocolitis [39]. When nivolumab is given as a single agent, median time to onset of immune-mediated colitis is 2.7–5.6 months, developing as early as 2 days and as late as 15 months [44]. The median time to onset of colitis with concurrent ipilimumab and nivolumab is shorter at 1.6 months [44]. The median time to onset of colitis is 3.4 months for pembrolizumab [45].

12.4.5 Management

Patients must be educated to report loose stools, diarrhea, and/or abdominal pain immediately to their physician and to track frequency. Thorough history and physical should be performed. Other possible causes of diarrhea should be assessed including viral gastroenteritis, medication-induced diarrhea, or infectious diarrhea. It is possible for patients to have a superimposed infection, such as clostridium difficile, with ICI-induced diarrhea/colitis. In patients who receive ICI, there should be a high index of suspicion for immune-related diarrhea and/or colitis. While small series have investigated the role of specific genomic variants that may predispose patients to the development of colitis, currently there is no test in clinical use [46], and there are no recommended preventative measures. In a phase II randomized study, prophylactic oral budesonide failed to prevent the onset of gastrointestinal irAEs in patients treated with ipilimumab compared with placebo [46].

Rapid treatment of ICI-mediated colitis is imperative. Delay of 3 weeks from the onset of symptoms to the initiation of steroid treatment has been linked to at least two colitis deaths [40, 47]. Initiation of steroid treatment within 5 days of the onset of ICI-mediated enterocolitis led to faster resolution of symptoms than when steroid was delayed >5 days [48].

Algorithms for the management of ICI-mediated diarrhea have been developed, and their use is recommended [35, 40]. Initial management for grade 1 diarrhea is symptomatic with encouragement of oral hydration, antidiarrheal medications such as loperamide, and electrolyte repletion. Patients should be monitored with vigilance for worsening diarrhea or development of colitis.

Grade 2 diarrhea is managed symptomatically initially with supportive care. ICI should be withheld. If diarrhea persists for greater than 3–5 days, prednisone or equivalent at 0.5–1 mg/kg/day should be administered. Oral diphenoxylate hydrochloride, atropine sulfate four times per day, and budesonide 9 mg once per day have been used by experienced practitioners to treat grade 2 diarrhea [40]. Referral to gastroenterologist for sigmoidoscopy or colonoscopy to diagnose colitis is indicated for persistent grade 2 diarrhea, grade 3–4 diarrhea, or rectal bleeding. The presence of any colitis mandates a course of systemic steroids. Treatment can be resumed upon resolution of symptoms after steroids have been tapered for at least 1 month.

Grade 3–4 diarrhea or colitis requires discontinuation of ICI. Admission to the hospital should be considered for intravenous steroids, intravenous fluids,

electrolytes, and careful monitoring. Prednisone or its equivalent of 1–2 mg/kg/day should be administered as soon as possible. Upon improvement to grade 1 or less, initiate corticosteroid tapers over at least 4 weeks to ensure complete resolution of symptoms. Resumption of ICI can be considered in grade 3 diarrhea or colitis when symptoms are grade 1 and steroids have been tapered for at least 1 month. Permanent cessation of ICI is recommended for grade 4 colitis, hemorrhage, or perforation.

For patients with refractory symptoms despite treatment with high-dose steroids for approximately 5 days, a single dose of infliximab 5 mg/kg has demonstrated rapid resolution of symptoms and durable efficacy [43, 49]. Infliximab may also be considered for persistent grade 2 symptoms that do not resolve despite treatment with steroids or with recurrence of symptoms and difficulty tapering off of steroids. Consider a surgical consult for patients with severe diarrhea/colitis or ileus early in the treatment course. Colitis can progress to intestinal perforation which can be fatal.

12.4.6 Time to Resolution

In patients with metastatic melanoma who developed grade 3–5 ipilimumab-mediated enterocolitis in a phase III trial, median duration of treatment with high-dose steroids was 16 days (ranging up to 3.2 months) followed by corticosteroid taper [39]. The median duration of pembrolizumab-mediated colitis is 1.4 months (range, 1 day to 7.2 months) [45]. Nivolumab-mediated colitis led to treatment with high-dose steroids for a median duration of 3 weeks to 4.2 months in various clinical trials followed by steroid taper [44].

12.5 Hepatotoxicity

12.5.1 Clinical Presentation

Hepatotoxicity is a less common but serious irAE characterized by immune-mediated hepatitis. In general, routine laboratory assessment will find elevations in serum levels of hepatic enzymes aspartate aminotransferase (AST) and alanine aminotransferase (ALT) and/or bilirubin. Most episodes are asymptomatic though associated fever, right upper quadrant pain, and malaise have been described. Concomitant elevations in total bilirubin can occur usually with prolonged transaminitis due to inflammation and cholestasis. Hyperbilirubinemia can cause jaundice, scleral icterus, and tea-colored urine.

12.5.2 Grading

Grade 1: AST and/or ALT >3.0 times the upper limit of normal, bilirubin >1.5 times the upper limit of normal

Grade 2: AST and/or ALT >3.0–5.0 times the upper limit of normal, bilirubin >1.5–3.0 times the upper limit of normal

Grade 3: AST and/or ALT >5.0–20.0 times the upper limit of normal, bilirubin >3.0–10.0 times the upper limit of normal
Grade 4: AST and/or ALT >20.0 times the upper limit or normal, bilirubin >10 times the upper limit of normal
Grade 5: Death

12.5.3 Time to Presentation

The median time to onset of grade 3–4 immune-mediated hepatitis was 2.0 months in patients receiving adjuvant ipilimumab for locally advanced melanoma. Lower grade 2 hepatitis occurred earlier at 1.4 months [39]. In patients treated with pembrolizumab, the median time to hepatitis onset is 26 days (range, 8 days to 21.4 months) [45]. In patients treated with nivolumab, the median time to hepatitis onset is 3.7 months (range, 6 days to 9 months) [44].

12.5.4 Incidence

A large meta-analysis revealed the incidence of all-grade and high-grade hepatotoxicity among patients treated with CTLA-4 inhibitors is 5% and 2%, respectively [4].

The combination of CTLA-4 and PD-1 blockade increases the risk of liver toxicity. For example, in melanoma patients treated with combined nivolumab plus ipilimumab, the rates of all-grade and high-grade transaminitis were 15.3% and 6.1%, respectively [26].

Compared to treatment with anti-CTLA-4 monotherapy and combined CTLA-4 and PD-1 checkpoint blockade, treatment with PD-1 inhibition results in the least hepatotoxicity. In a large phase III clinical trial of NSCLC patients, the use of pembrolizumab resulted in elevated liver enzymes in 3.0% and severe hepatotoxicity in 0.6% of patients [6]. In a pooled analysis of four clinical trials utilizing nivolumab in advanced melanoma, liver toxicity of all grades was reported in 4% of patients [25].

12.5.5 Management

Current guidelines recommend evaluation of hepatic enzymes (AST, ALT, alkaline phosphatase, bilirubin) at baseline, prior to each dose, and periodically after completion of therapy. Patients should be counseled to minimize intake of other hepatotoxic medications such as alcohol or excessive acetaminophen. It is reasonable to check baseline viral hepatitis serologies prior to administration of ICI, particularly in patients with identified risk factors. Most clinical trials excluded patients with active hepatitis B or C though use of ICI in a small series of patients with active hepatitis B or C has yielded similar hepatotoxicity to the general population [50].

Management algorithms have been developed and are recommended [35, 39, 40]. For grade 1 hepatotoxicity, ICI can be continued. Monitoring should increase with laboratory drawings at least twice weekly. Work-up for autoimmunity should be considered, including serum antinuclear antibody, smooth muscle antibody, anti-mitochondrial antibodies, anti-liver–kidney microsomal-1 antibodies, and others as appropriate. Viral hepatitis panels should be performed if not already completed. Liver imaging should be performed to rule out obstruction or disease progression as possible confounding diagnoses. Alcohol consumption should be quantified and intake should be stopped.

For grade 2 hepatotoxicity, ICI should be held. Liver enzymes should be tested at least every 3 days. A dose of 0.5 to 1 mg/kg/day prednisone equivalents should be administered. ICI can be resumed upon resolution to grade 1 toxicity once steroids have been tapered for at least 1 month. Autoimmune work-up as above is recommended.

For grade 3 or 4 hepatotoxicity, ICI should be held. Administer corticosteroids at a dose of 1–2 mg/kg/day prednisone equivalents. Admission to the hospital for 24–48 h of IV steroids should be considered. Liver enzymes should be checked daily until improvement is ensured. It is recommended in grade 3 or 4 hepatotoxicity that ICI is held indefinitely. Steroids should be tapered over at least 1 month. If liver enzyme elevations persist, worsen, or rebound for greater than 3–5 days, non-corticosteroid immunosuppressive medications such as oral mycophenolate mofetil should be administered [40]. Infliximab should be avoided due to its potential for hepatotoxicity. Anti-thymocyte globulin (ATG) has been used in a severe steroid and mycophenolate mofetil refractory case of autoimmune hepatitis [51].

12.5.6 Time to Resolution

With ipilimumab treatment for melanoma, patients were treated for grade 3–4 hepatitis with systemic corticosteroids for a median of 4.4 months (ranging up to 56.1 months). Patients with moderate hepatitis were treated with systemic corticosteroids for a median duration of 2.6 months (ranging up to 41.4 months) [39]. In patients treated with nivolumab, hepatotoxicity treated with high-dose corticosteroids led to resolution in a median of 3–4 weeks (range, 5 days to 2 months) [25, 44].

12.6 Pneumonitis

12.6.1 Clinical Presentation

Although rare, pneumonitis is a feared complication of ICI. It should be suspected when a patient on an immune checkpoint inhibitor develops a nonproductive cough, progressive shortness of breath, fine crackles on examination, and hypoxia. CT imaging of pneumonitis shows a spectrum of findings typically seen in interstitial

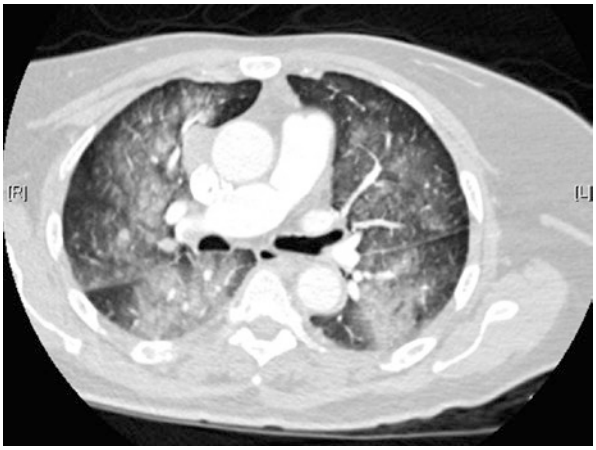

Fig. 12.4 Pneumonitis in a patient with metastatic melanoma. This is a patient who received two cycles of an anti-PD-1 antibody and subsequently presented with hypoxia, dyspnea, and cough. CT scan demonstrated new diffuse bilateral ground-glass opacities, concerning for drug-induced pneumonitis

pneumonias including diffuse ground-glass opacities and reticular opacities in the peripheral and lower lungs [52]. The primary differential diagnoses include infection, progression of disease, and pulmonary edema (Fig. 12.4).

12.6.2 Grading

Grade 1: Asymptomatic; clinical or diagnostic observations only; intervention not indicated
Grade 2: Symptomatic; medical intervention indicated; limiting instrumental ADL
Grade 3: Severe symptoms; limiting self-care ADL; oxygen indicated
Grade 4: Life-threatening respiratory compromise; urgent intervention indicated (e.g., tracheostomy or intubation)
Grade 5: Death

12.6.3 Incidence

In randomized phase II and phase III trials, the incidence of all-grade pneumonitis in patients treated with ipilimumab ranged from 0.4% to 1.6%. High-grade pneumonitis occurred in 0.3–0.4% of patients that received ipilimumab [5, 53, 54]. These numbers do not include data from a relatively small randomized phase III study by Postow et al., in which 142 patients with advanced melanoma were randomized 2:1 to ipilimumab combined with nivolumab vs. ipilimumab combined with placebo. In this trial, the rates of all-grade and high-grade pneumonitis in the ipilimumab

monotherapy arm (4% all grade, 2% high grade) were about four times as high as the incidence of pneumonitis observed with ipilimumab in other trials [55].

Randomized phase II and phase III studies of nivolumab have demonstrated incidence of all-grade pneumonitis between 1.3% and 5% and high-grade pneumonitis between 0% and 1% in treated patients [12–14, 24, 56]. Phase II and III trials of pembrolizumab show similar rates of all-grade (0.4–5%) and high-grade (0–2%) pneumonitis [5, 7].

Combining ipilimumab with nivolumab increases toxicity. In two-phase III trials, all-grade and high-grade pneumonitis occurred in 6.4–11% and 1–2%, respectively, of patients treated with both ipilimumab and nivolumab. There was also one death due to drug-related pneumonitis in the combination arm [54, 55]. A meta-analysis of randomized phase II and III studies of ipilimumab, nivolumab, and pembrolizumab in patients with solid tumors revealed that compared to treatment with ipilimumab alone, combining ipilimumab with nivolumab increases the incidence of all-grade pneumonitis but is not associated with increased risk of high-grade pneumonitis (OR of all-grade pneumonitis with nivolumab/ipilimumab vs. ipilimumab monotherapy is 3.68 [95% CI 1.59–8.50, $p = 0.002$]). OR for high-grade pneumonitis is 1.86 [95% CI 0.36–9.53, $p = 0.46$] [57].

The same meta-analysis demonstrated no difference in the risk of either all-grade or high-grade pneumonitis between PD-1 inhibitors and ipilimumab (OR for all-grade pneumonitis 1.26, 95% CI 0.44–3.63, $p = 0.66$. OR for high-grade pneumonitis 0.71, 95% CI 0.10–5.08, $p = 0.74$). Similarly, there was no difference in risk of pneumonitis according to type of cancer treated (NSCLC vs. other cancer) (OR for all-grade pneumonitis 3.96, 95% CI 2.02–7.79, $p < 0001$. OR for high-grade pneumonitis 2.87, 95% CI 0.90–9.20, $p = 0.08$) [57].

12.6.4 Timing of Onset

Only two of the phase II and III trials of ipilimumab, nivolumab, and pembrolizumab describe the timing of onset of pneumonitis. Both of these studies were phase III randomized trials investigating nivolumab in patients with advanced NSCLC. In one of these trials, the median time to onset of treatment-related pneumonitis was 15.1 weeks (ranged, 2.6–85.1 weeks) [13]. In the second study, median time to onset was 31.1 weeks (range, 11.7–56.9 weeks) [12]. Based on these data, pneumonitis usually occurs within the first 3–6 months of treatment with a checkpoint inhibitor but can occur at any time.

12.6.5 Management

There are no formal guidelines for the management of ICI-mediated pneumonitis. ICI should be held in all cases of suspected pneumonitis. Bronchoscopy with bronchoalveolar lavage and transbronchial biopsy of a lymph node can be useful to rule out infection or progression of metastatic disease as alternative diagnoses. Empiric

antibiotics should also be considered. For grade ≥2 pneumonitis, steroids (e.g., prednisone 1–2 mg/kg/day PO or methylprednisolone 1–2 mg/kg/day IV) are the mainstay of treatment. If symptoms improve on steroids, a gradual taper over several weeks is recommended. If there is no improvement after 48–72 h on steroids, additional immunosuppressive therapy, such as infliximab, should be considered [55, 58].

12.6.6 Time to Resolution

In phase II and III clinical trials, pneumonitis resolved with treatment in 66.7–100% of cases. Median time to resolution varied from 3.2 to 6.1 weeks [12, 13, 54, 55].

12.7 Endocrine Toxicity

12.7.1 Thyroid Dysfunction

12.7.1.1 Clinical Presentation

ICI can cause a number of different thyroid disorders including primary hypothyroidism due to destructive thyroiditis (high TSH, low free T4), secondary hypothyroidism as a result of hypophysitis (low TSH, low free T4), acute thyroiditis with transient hyperthyroidism (low TSH, high free T4) followed by hypothyroidism (high TSH, low free T4), and hyperthyroidism associated with Graves' disease (low TSH, high free T4). Symptoms are non-specific and may include fatigue, weight change, temperature intolerance, constipation, diarrhea, bradycardia, and/and tachycardia, depending on the direction and degree of thyroid hormone imbalance [58–60].

Because hypo- and hyperthyroidism are relatively common side effects of immune checkpoint blockade and are associated with non-specific symptoms, TSH and free T4 should be monitored at baseline, periodically throughout treatment and more frequently if clinically indicated.

12.7.1.2 Grading

Grade 1: Asymptomatic; clinical or diagnostic observations only; intervention not indicated
Grade 2: Symptomatic; thyroid replacement (hypothyroidism) or suppression therapy (hyperthyroidism) indicated; limiting instrumental ADL
Grade 3: Severe symptoms; limiting self-care ADL; hospitalization indicated
Grade 4: Life-threatening consequences; urgent intervention indicated
Grade 5: Death

12.7.1.3 Incidence

Thyroid dysfunction is more common with PD-1 blockade than CTLA-4 inhibition, and hypothyroidism occurs more often than hyperthyroidism. In phase II and III trials, all-grade hypothyroidism was reported in 4–8.6% of patients treated with

nivolumab [12, 13, 24, 54], 7–10% of patients who received pembrolizumab [5–7, 61], and 1.5–4.2% of patients on ipilimumab [2, 5, 54]. In those same trials, all-grade hyperthyroidism developed in 3.4–4.2% of nivolumab patients [24, 54], 4–6.5% of patients treated with pembrolizumab [5, 7, 61], and 1–2.3% of patients that received ipilimumab [5, 54]. Although fairly common, both hypo- and hyperthyroidism are usually mild, and rates of high-grade (grade 3–4) thyroid dysfunction are low (0–0.4%) [5–7, 12, 13, 24, 54, 57, 61]. The combination of nivolumab and ipilimumab increases the rates of all-grade hypothyroidism (15–16%) and hyperthyroidism (4.3–9.9%) but does not appear to increase the risk of high-grade thyroid disorders (0–1%) [54, 62].

12.7.1.4 Timing of Onset

The onset of ICI-mediated thyroid dysfunction varies from within 4 weeks of initiation of therapy to 3 years. In general, acute thyroiditis and hyperthyroidism occur early in treatment (median time of onset 4–6 weeks), and hypothyroidism occurs a little later (median time of onset 12 weeks) [63, 64].

12.7.1.5 Management

As noted above, thyroid dysfunction is usually mild and rarely an indication for interrupting or discontinuing ICI. Hypothyroidism should be managed with levothyroxine thyroid hormone replacement, initiated at a dose of 1–1.5 mcg/kg and titrated to TSH levels of 1–2 mU/l. Hyperthyroidism may resolve spontaneously, but patients should be monitored carefully for the development of subsequent hypothyroidism. If the patient is symptomatic, a steroid burst could be considered for acute thyroiditis. A nonselective beta-blocker, such as propranolol, could also be started for tachycardia. If hyperthyroidism persists, endocrinology should be consulted for management guidance and recommendations regarding role for thyroid suppression therapy, such as methimazole [58–60].

12.7.1.6 Time to Resolution

When it occurs as a side effect of ICI, hypothyroidism is usually permanent. By contrast, hyperthyroidism resolves in most patients. The time to resolution of immune-related thyroid dysfunction has not been well studied, but a pooled analysis of endocrine side effects in several pivotal PD-1 trials demonstrated a median time to resolution of 20.6 weeks (range 0.4–47.6; $n = 6$) [63].

12.7.2 Hypophysitis

12.7.2.1 Clinical Presentation

Hypophysitis, or inflammation of the pituitary gland, can present with a range of symptoms related to both mass effect and hormonal deficiencies resulting from anterior hypopituitarism. The most common initial symptoms are new-onset headache, fatigue, and asthenia. Other symptoms may include anorexia, nausea, vomiting, diarrhea, constipation, temperature intolerance, decreased libido, erectile

dysfunction, confusion, and mental status changes [65, 66]. Based on several series, hypocortisolism (60–100% of cases), hypothyroidism (60–100% of cases), and hypogonadism (71–87% of cases) are usually present. Prolactin and growth hormone levels are usually normal but have been reported to be abnormally high or low in up to 25% of patients [4, 67–70]. Visual disturbances due to pituitary swelling are rare [67]. A few cases of diabetes insipidus have been reported [65, 70]. Brain MRI is important to rule out sellar metastatic disease as a cause of the patient's presentation. Classic MRI findings include symmetric enlargement and homogeneous enhancement of the pituitary gland, but a normal MRI does not rule out hypophysitis [67]. Interestingly, there appears to be a male predominance of checkpoint inhibitor-associated hypophysitis (~6:1, male/female). However, the true male/female distribution is unknown because the sex of patients with hypophysitis is not reported in several studies. Furthermore, this apparent finding may be partially explained by the higher incidence of metastatic melanoma in men [71].

12.7.2.2 Grading

Hypophysitis is not an adverse event specifically defined by CTCAE version 4. However, the toxicity grading structure for "endocrine disorders—other" has been applied to hypophysitis and is listed below.

Grade 1: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2: Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental ADL
Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL
Grade 4: Life-threatening consequences; urgent intervention indicated
Grade 5: Death

12.7.2.3 Incidence

Hypophysitis is a relatively uncommon complication of ICI that is most often associated with CTLA-4 inhibition and rarely occurs with PD-1 blockade. For example, in randomized phase II and III trials, all-grade hypophysitis was reported in 1.5–3.9% of patients receiving ipilimumab [2, 5, 54], compared to 0.6% of patients on nivolumab [54] and <1–0.7% of patients treated with pembrolizumab [5, 7, 61]. Rates of high-grade hypophysitis in these trials were lower but had a similar distribution (ipilimumab 1.5–1.9% vs. nivolumab 0.3% vs. pembrolizumab <1%) [2, 5, 7, 54, 61]. The combination of ipilimumab and nivolumab increases the risk of hypophysitis (all grade 7.7–12%, high grade 1.6–2%) [54, 62].

12.7.2.4 Timing of Onset

The median time of onset of hypophysitis is 9–16 weeks following initiation of checkpoint blockade, but cases have been reported as early as 4 weeks and as late as 19 months after starting treatment [40, 64, 65, 67, 70, 72].

12.7.2.5 Management

High index of suspicion is needed for diagnosis of all endocrine irAEs. The diagnosis of hypophysitis is established by low levels of all or several of the hormones produced by the anterior pituitary including thyroid-stimulating hormone (TSH), free T4, adrenocorticotropic hormone (ACTH), morning cortisol, follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol in females, testosterone in males, growth hormone (GH), IGF-1, and prolactin. Brain MRI is recommended to evaluate for enlargement and enhancement of the pituitary and rule out sellar metastatic disease. Brain MRI may be normal in the presence of hypopituitarism.

There are no formal guidelines for the management of ICI-mediated hypophysitis. Treatment primarily involves high-dose steroids, replacement of the affected pituitary hormones, and consideration of ICI discontinuation. Multidisciplinary management, in conjunction with an endocrinologist, is critical. Once symptoms are managed and the patient is on stable doses of steroids, ICI can often be resumed.

For grade 1 hypophysitis, some authors have recommended continuation of ICI with close observation for 1 week and initiation of high-dose corticosteroids (e.g., prednisone or solumedrol 1 mg/kg/day) if symptoms persist after that time [73].

For grade ≥2 hypophysitis, conventional recommendations have been to hold ICI until all adverse events resolve to grade 1 or less, initiate high-dose corticosteroids, and replace deficient pituitary hormones. However, both the recommendation to discontinue ICI and the role for high-dose steroids have been questioned recently, following one cohort study in which most patients continued ICI with concurrent hormone replacement [72] and two cohort studies that suggested steroids did not improve pituitary function recovery [70, 72]. If high-dose steroids are used, they should be tapered gradually to physiologic replacement doses of hydrocortisone (see below) [74, 75].

Finally, replacement of the affected hormones should be done under the guidance of an endocrinologist. In general, hydrocortisone (20 mg morning, 10 mg evening) is typically used to treat secondary adrenal insufficiency resulting from hypopituitarism. In contrast to primary adrenal insufficiency, mineralocorticoid replacement is usually not necessary. Hypothyroidism is treated with levothyroxine. Importantly, levothyroxine should not be administered until adrenal insufficiency has been treated because treatment of hypothyroidism alone in a patient with coexisting hypothyroidism and adrenal insufficiency can increase the severity of the cortisol deficiency. Treatment of LH and FSH deficiency depends on gender and fertility goals [58, 76, 77].

12.7.2.6 Time to Resolution

Adrenal insufficiency associated with ICI-mediated hypophysitis is usually permanent, and most patients require lifelong glucocorticoid replacement. To date, only a handful of cases of corticotroph recovery have been reported [74, 78]. By contrast, recovery of thyroid function occurs in 37–50% of patients [40, 67, 70], and gonadal function returns in 57% of men [67, 79]. The median time to resolution of hypothyroidism and hypogonadism was 13 and 10 weeks, respectively, in one study [70]. The time to resolution of MRI findings varies and has been reported as early as 2 weeks and as late as 27 weeks [70, 74].

12.8 Hematologic Toxicity

12.8.1 Clinical Presentation

Rare immune-related hematologic toxicities have been reported with CTLA-4 inhibition including thrombocytopenia, neutropenia, acquired hemophilia A, and red cell aplasia. Minor decreases and fluctuations in cell counts are common in patients with advanced cancer. However, these immune-related phenomena are profound and persistent without treatment.

Pure red cell aplasia presented in the setting of ipilimumab with an isolated anemia and low reticulocyte count in the absence of bleeding or hemolysis. Other cell lines including platelets and white blood cells were grossly normal. Peripheral blood film revealed normochromic and normocytic red blood cells with marked anemia. Bone marrow biopsy showed marked erythroid hypoplasia, granulocytic hyperplasia, and adequate maturing megakaryocytes without myelodysplasia, malignancy, or parvovirus [80].

Severe neutropenia during treatment with ICI has been described in a case report. Bone marrow aspiration and biopsy revealed marked myeloid hypoplasia with unremarkable erythropoiesis and megakaryopoiesis [81].

Acquired hemophilia caused by the presence of an acquired factor VIII inhibitor has been seen in a patient treated with CTLA-4 inhibition. The clinical presentation started with hematuria and isolated prolongation of activated partial thromboplastin time. Factor VIII inhibitor was confirmed with a factor VIII level <1% and inhibitor titer of 26 Bethesda units [82].

Grade 4 immune-mediated thrombocytopenia has also been described with ipilimumab. Bone marrow biopsy revealed increased megakaryocytes supporting a diagnosis of drug-induced immune-mediated thrombocytopenia [83].

12.8.2 Grading

Grade 1: Hgb <LLN–10.0 g/dL; <LLN–75,000/mm^3; <LLN–1500/mm^3
Grade 2: Hgb <10.0–8.0 g/dL; <75,000–50,000/mm^3; <1500–1000/mm^3
Grade 3: Hgb <8.0 g/dL; <50,000–25,000/mm^3; <1000–500/mm^3
Grade 4: Life-threatening consequences; urgent intervention indicated; <25,000/mm^3; <500/mm
Grade 5: Death

12.8.3 Incidence

Grade 1 or 2 anemia has been reported in up to 4.2% of patients with ICI [6]. It is not clear if this is due to the effects of ICI or variable other causes of anemia. Grade 3 or 4 anemia is rarely reported. Anemia and neutropenia are much more common with the use of cytotoxic chemotherapy. For example, a large phase III clinical trial in patients with advanced non-squamous NSCLC showed an incidence of all-grade anemia in 2% versus 20% of patients with nivolumab and docetaxel, respectively [12].

All-grade neutropenia in the same trial showed an incidence of <1% versus 31% in nivolumab and docetaxel groups [12].

Grade 3 or 4 immune-mediated hematologic toxicity is rare and occurs in far less than 1% of patients treated with anti-PD-1 or anti-CTLA-4 mAbs.

12.8.4 Time to Presentation

Hematologic presentations are rare and a specific time to presentation has not been reported.

12.8.5 Management

Complete blood count (CBC) assessment is recommended prior to initiation of ICI and prior to each dose. Any abnormality should prompt closer interval evaluation. As previously mentioned, minor fluctuations in cell lines, particularly anemia, are common in advanced cancer. Grade 1–2 anemia is commonly reported in clinical trials and does not require treatment or cessation of ICI. Routine investigation of all hematologic toxicity for alternate etiologies is initially recommended.

Immune-related anemia, thrombocytopenia, and neutropenia are usually profound (grade 3 or 4). Isolated anemia should be evaluated comprehensively ruling out other etiologies such as hemorrhage, hemolysis, vitamin or iron deficiencies, and thyroid disorders. Peripheral blood film is useful initially. Supportive care and blood transfusion as needed are recommended. If underlying cause cannot be found, bone marrow biopsy is useful to rule out bone marrow involvement from malignancy, myelodysplastic syndrome especially in patients exposed to prior chemotherapy or radiation, or pure red cell aplasia.

If immune-related etiology of anemia is suspected, prednisone 1–2 mg/kg/day or equivalent can be administered. ICI should be withheld for grade 3 or 4 hematologic toxicity. If no improvement is seen within several days, intravenous immunoglobulin (IVIG) led to rapid reticulocytosis and normalization of hemoglobin in pure red cell aplasia caused by ipilimumab refractory to steroids.

Leukopenia, thrombocytopenia, and neutropenia found on routine CBC should be evaluated for other causes including medications, infection, disseminated intravascular coagulation, etc. Bone marrow biopsy should be considered. Patients should be instructed to monitor their temperature and seek immediate medical care for fever in the setting of neutropenia. If immune-mediated etiology is suspected, prednisone 1–2 mg/kg/day or equivalent should be administered for grade 3 or 4 hematologic toxicity. When neutropenia or thrombocytopenia does not respond to steroids, IVIG rapidly improved immune-related anemia, neutropenia, and thrombocytopenia in case reports [80, 81, 83].

12.8.6 Time to Resolution

Immune-related red cell aplasia and neutropenia improved rapidly upon administration of IVIG. Thrombocytopenia resolution began improving after 9 days of therapy.

12.9 Ocular Toxicity

12.9.1 Clinical Presentation

Ocular adverse events are rare but have been reported with ICI, especially ipilimumab. A variety of inflammatory conditions involving different ocular locations have been described in case reports and series of patients treated with ipilimumab including conjunctivitis, bilateral anterior uveitis, vitritis, papillitis, choroiditis, serous retinal detachment, peripheral ulcerative keratitis (PUK), inflammatory orbitopathy, choroidal neovascularization, neuroretinitis, orbital myositis, and bilateral optic neuropathy [84]. Bilateral anterior uveitis with neuroretinitis presented as unilateral metamorphopsias (distorted vision in which grid of straight lines appears wavy), scotoma, bilateral eye pain, redness, and photophobia [84]. Comprehensive ophthalmologic exam revealed anterior chamber inflammation and bilateral optic nerve edema. Bilateral uveitis alone presented with blurred vision, flashes, floaters, and headache [85]. Development of uveitis is often associated with ICI-related colitis. Inflammatory orbitopathy presented with tearing, diplopia, pain, conjunctival chemosis, and limitation in extraocular motility [85]. PUK presented with bilateral eye pain.

Ocular toxicity is rare with PD-1 inhibition but has been described in case reports describing uveitis [86, 87].

12.9.2 Grading

Eye disorders:

Grade 1: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2: Moderate; minimal, local, or noninvasive intervention indicated; limiting safe-appropriate instrumental ADL
Grade 3: Severe or medically significant but not immediately sight-threatening; hospitalization indicated; disabling; limiting self-care ADL
Grade 4: Sight-threatening consequences; urgent intervention indicated; blindness (20/200 or worse) in the affected eye

12.9.3 Incidence

The incidence of ocular irAEs in ipilimumab phase II and III trials was 1.3%, with 0.4% being grade 3 or higher [88]. The incidence of ocular events in clinical trials using anti-PD-1 mAbs is not well described but is less than 1%.

12.9.4 Time to Presentation

The majority of patients developed ocular irAEs after second or third dose of ipilimumab [85].

12.9.5 Management

Treatment of ipilimumab-associated ocular irAEs depends on the severity and location of inflammation and presence of systemic complications. Topical corticosteroid drops are sufficient in mild cases of anterior uveitis, iritis, episcleritis, and PUK [84, 85]. Posterior uveitis or sight-threatening orbital inflammation warrants systemic corticosteroids [84, 85]. Prompt referral to an ophthalmologist should be made for any visual complaints. MRI brain should be considered to rule out central nervous system metastatic disease when symptoms such as diplopia, headache, or blurred vision occur. Thyroid and adrenal function tests should be performed in the case of orbital inflammation.

Ocular irAEs from ipilimumab usually resolve with corticosteroid treatment. Permanently discontinue ICI for immune-mediated ocular disease that is unresponsive to local immunosuppressive therapy [39].

12.9.6 Time to Resolution

Ocular irAEs usually resolve with topical or systemic corticosteroids. Uveitis and PUK resolved within 1–6 weeks [85]. Inflammatory orbitopathy took several months to resolve.

12.10 Rheumatologic Toxicity

12.10.1 Clinical Presentation

Joint and muscular pain is often described with ICI. Arthralgias are commonly reported with anti-PD-1 mAbs and can present as monoarticular or polyarticular joint pain. Polyarticular inflammatory arthritis has been described with pembrolizumab use. This can present as severe tenosynovitis, synovitis, and/or myositis [89]. Changes to the joint including redness, erythema, and swelling are concerning for inflammatory arthritis.

Myalgias are the second most commonly reported musculoskeletal toxicity. Myalgias present as muscular pain, which can be diffuse or localized. Rare cases of severe autoimmune inflammatory myopathy and necrotic myositis have been described with ipilimumab and pembrolizumab therapy [90, 91].

An array of other immune-related rheumatologic toxicities have been reported in less than 1% of patients treated with ICI including as polymyalgia rheumatic/giant cell arteritis, sarcoid-like reaction [92–95], and vasculitis (granulomatosis with polyangiitis) [96].

Polymyalgia rheumatica has occurred in several patients on ipilimumab therapy presenting as pain, stiffness, and/or weakness involving the proximal muscles of the neck, shoulders, upper arms, and hips [97]. Both cases were associated with giant cell arteritis (GCA) which is a vasculitis involving the large and medium arteries of the head. Inflammatory markers including erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are usually elevated.

Sarcoidosis has presented in a variety of ways including cutaneous, pulmonary, and splenic lesions. Biopsy is needed to differentiate sarcoidosis from disease progression.

12.10.2 Grading

Arthralgia:

Grade 1: Mild pain
Grade 2: Moderate pain; limiting instrumental ADL
Grade 3: Severe pain; limiting self-care ADL

Myositis:

Grade 1: Mild pain
Grade 2: Moderate pain associated with weakness; pain limiting instrumental ADL
Grade 3: Pain associated with severe weakness; pain limiting self-care ADL

12.10.3 Incidence

In clinical trials using anti-PD-1 mAbs in patients with diverse malignancies, the incidence grade 1–2 arthralgia is 5–17% with high-grade arthralgia in less than 1% of patients [5, 6, 11, 13]. The incidence of low-grade and high-grade myalgias in these same trials was <1.0–15% and less than 1%.

The incidence of arthralgia with ipilimumab therapy in a clinical trial of patients with advanced melanoma was 5.1% and <1% for low grade and high grade, respectively [5].

Autoimmune inflammatory myositis, PMR/GCA, vasculitis, and sarcoidosis are rare events occurring in less than 1% of patients.

12.10.4 Time to Presentation

Time to presentation has not been reported.

12.10.5 Management

There are no specific management guidelines for rheumatologic adverse events. Grade 1–2 musculoskeletal AEs including myalgias and arthralgias can be treated initially with nonsteroidal anti-inflammatory drugs. Synovitis and tenosynovitis have been treated symptomatically with bisphosphonates and sulfasalazine [89]. If this is not sufficient, systemic prednisone starting at 0.5 mg/kg or equivalent can be

administered. Tapering of steroids should begin after relief of symptoms is attained. Laboratory studies including ESR and CRP should be obtained and trended to assess the degree of inflammation and treatment response.

For arthralgia specifically, it is reasonable to obtain a rheumatoid factor, anti-citrullinated antibody, antinuclear antibody, uric acid to assess for development of specific rheumatologic syndromes including rheumatoid arthritis, systemic lupus erythematosus, and gout. Referral to a rheumatologist is highly recommended with the development of an autoimmune musculoskeletal disorder or polyarticular arthritis with joint changes.

In the case of myalgia or myositis, serum creatinine kinase should be assessed to rule out inflammatory myositis or rhabdomyolysis. The mainstay of treatment for myositis is glucocorticoid therapy initiated with prednisone at a dose of 1 mg/kg per day followed by a slow taper. Inflammatory myopathy can occur in the setting of thyroid and adrenal dysfunction; therefore, these serologic tests should be evaluated.

12.10.6 Time to Resolution

Time to resolution has not been specifically reported.

12.11 Neurologic Toxicity

12.11.1 Clinical Presentation

Neurological irAEs are a rare heterogeneous toxicity class of ICI. A variety of neurologic syndromes have been described with anti-CTLA-4 mAbs such as Guillain-Barre´ syndrome (GBS) [98], aseptic meningitis [99], posterior reversible encephalopathy syndrome (PRES) [100], myasthenia gravis (MG)-type syndrome [101], mono- or polyneuropathy [102], inflammatory enteric neuropathy [103], limbic encephalitis, chronic inflammatory demyelinating polyneuropathy (CIDP) [101], and transverse myelitis [101]. Encephalitis associated with Hashimoto's thyroiditis has also been described [89]. Limbic encephalitis [72], myasthenia gravis [93], peripheral neuropathy, and GBS have occurred in patients receiving PD-1 inhibition.

GBS presented as numbness and tingling in the hands and feet that rapidly ascended to loss of sensory and motor function of the limbs impairing gait. Clinical neurological examination revealed a loss of the deep tendon reflexes. Electromyography (EMG) was a diagnostic for a generalized motor and sensory demyelinating polyneuropathy. Cerebrospinal fluid (CSF) analysis showed an elevated protein level and IgG with the presence of oligoclonal bands in CSF and serum [98].

PRES presented as acute bilateral blindness with headache and generalized tonic-clonic seizure in a hospitalized patient with acute renal failure. MRI brain

showed multiple bilateral symmetric alterations in the cortical and subcortical areas in the parieto-occipital region, frontal and temporal lobes, and cerebellar hemispheres [100].

MG presented with concurrent myositis. Initial symptoms included dysphagia, odynophagia, bilateral ptosis, fatigability/weakness of the proximal muscles in the setting of elevated acetylcholine receptor-binding Ab, acetylcholine receptor-modulating Ab, and anti-striated muscle Ab [101].

Inflammatory enteric neuropathy presented as severe refractory constipation [103]. Colonoscopy with biopsies was performed revealing prominent inflammatory infiltrates of mononuclear lymphocytes associated with the myenteric nervous system.

CIDP presented as proximal muscle weakness and intermittent numbness and tingling in the face and upper and lower extremities bilaterally. Initially symptoms were intermittent but then became constant [101]. Transverse myelitis presented as bilateral lower extremity weakness and paresthesias with intermittent urinary retention and fecal incontinence [101].

12.11.2 Grading

Due to the wide variety of neurological events described, please see the Common Terminology Criteria for Adverse Events (CTCAE) for specific grading.

12.11.3 Incidence

In a large phase III clinical trial of patients receiving ipilimumab in the adjuvant setting for high-risk melanoma, neurologic events occurred in 2.3% of patients [3] . Grade 3–5 neurologic AEs occur in less than 1%.

Neurologic AEs occur in less than 1% of patients treated with anti-PD-1 mAbs. One case of fatal limbic encephalitis has occurred with nivolumab [72].

12.11.4 Time to Presentation

Median time to presentation of neurologic AE with ipilimumab therapy was 13.1 weeks (8.3–77.3 weeks) [3]. Time to presentation for PD-1-mediated neurologic complications has not been described.

12.11.5 Management

Withhold ICI in patients with new-onset grade 3 or 4 neurologic signs or symptoms. Thorough history and physical should be performed to evaluate infectious or other causes of moderate-to-severe neurologic deterioration. Evaluation should include

neurologic consultation and brain imaging including MRI as soon as possible. Lumbar puncture can be helpful in evaluating infectious diseases, leptomeningeal metastatic disease, paraneoplastic syndromes, and inflammatory etiologies.

If other etiologies are ruled out, administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents for patients with grade 3 or 4 neurologic toxicity, followed by prolonged corticosteroid taper over at least 4 weeks. Permanently discontinue ICI for immune-mediated encephalitis, severe or life-threatening neurologic events defined as grade 3 or 4. Plasma exchange or IVIG may be considered for severe immune-mediated neurologic syndromes including GBS, MS, or CIPD, though limited data exists regarding the management of steroid-refractory neurologic irAEs [101].

12.11.6 Time to Resolution

Median time to resolution of ipilimumab-mediated neurologic toxicity was 8 weeks [3].

12.12 Renal Toxicity

12.12.1 Clinical Presentation

Acute renal failure due to immune-related nephritis has occurred rarely with ICI [104–106]. Minor fluctuations in serum creatinine can occur commonly through the duration of therapy. Immune-mediated nephritis is defined as renal dysfunction or serum creatinine 2–3 times above baseline increased creatinine, requirement for corticosteroids, and no clear alternate etiology [72]. The most typical clinical presentation is acute impairment of renal function seen by elevation in serum creatinine found on routine evaluation with or without an abnormal urinalysis.

Nephritis has been linked to either membranous lupus nephritis or more commonly acute interstitial granulomatous nephritis [105, 106]. Lupus nephritis has been described in a case report presenting with elevated serum creatinine, elevated urine protein excretion by spot urine protein-to-creatinine ratio, microscopic hematuria, elevated antinuclear antibodies (ANA) and anti-double-stranded DNA antibodies (dsDNA), and low complement (C3 and C4) levels. Kidney biopsy revealed extra-membranous and mesangial deposits of IgG, IgM, C3, and C1q [106].

Several cases of acute granulomatous interstitial nephritis have been described characterized by elevation in serum creatinine. Kidney biopsy revealed severe interstitial inflammation with edema or acute interstitial nephritis with tubular necrosis and non-necrotizing epithelioid granulomas [105]. There is lack of nephrotic range proteinuria, antinuclear antibodies, anti-double-stranded DNA antibodies, or microscopic hematuria. Kidney failure was preceded or accompanied with a rash in half of the cases. In one instance of ipilimumab-related renal failure, CT scan of the abdomen and pelvis revealed bilateral swelling of the renal cortices [104].

12.12.2 Grading

Acute kidney injury:

Grade 1: Creatinine level increase of >0.3 mg/dL; creatinine 1.5–2.0 times above baseline
Grade 2: Creatinine level 2–3 times above baseline
Grade 3: Creatinine greater than 3 times baseline or greater than 4.0 mg/dL; hospitalization indicated
Grade 4: Life-threatening consequences; dialysis indicated
Grade 5: Death

12.12.3 Incidence

The incidence of immune-mediated nephritis and renal failure with single-agent anti-CTLA-4 and anti-PD-1 mAbs is less than 1%. Immune-mediated nephritis and renal dysfunction occurred in 2.2% of patients receiving combined nivolumab and ipilimumab [72].

12.12.4 Time to Presentation

The time for renal disease to appear varied from 6 to 12 weeks in patients treated with ipilimumab therapy [105]. The median time to onset of nivolumab immune-mediated nephritis and renal dysfunction was 15 weeks [25]. The median time to onset of pembrolizumab immune-mediated nephritis was 5.1 months (range, 12 days to 12.8 months) [45].

12.12.5 Management

Kidney function should be evaluated prior to initiation and prior to each dose of ICI. Detection of any decreased renal function by laboratory evaluation should prompt closer monitoring. Urinalysis for detection of proteinuria and microscopic hematuria should be performed. It is very important to rule out other causes of renal failure including volume depletion, nephrotoxic medications, and urinary obstruction from malignancy. Nephrology consult is recommended. Quantitative evaluation of urine protein excretion should be performed with spot protein/creatinine ratio. Serum ANA, compliment levels, and dsDNA are recommended if lupus nephritis is suspected. Renal biopsy should be highly considered to differentiate etiologies.

Moderate (grade 2) or severe (grade 3) increased serum creatinine should be treated with corticosteroids at a dose of 0.5 to 1 mg/kg/day prednisone equivalents followed by corticosteroid taper. ICI should be withheld. If worsening or no

improvement occurs, increase dose of corticosteroids to 1 to 2 mg/kg/day prednisone equivalents and permanently discontinue ICI.

For life-threatening (grade 4) increased serum creatinine, patients should present to the emergency room or be directly admitted for electrolyte management, emergent nephrology consultation, and consideration of dialysis. Permanently discontinue ICI, and administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents followed by corticosteroid taper for at least 4 weeks.

12.12.6 Time to Resolution

Acute granulomatous interstitial nephritis resolved in most cases within 2–4 weeks of steroid treatment [105]. In patients who developed immune-mediated nephritis treated with nivolumab, high-dose corticosteroids were given for a median duration of 16 days (range, 1 day to 9.9 months). Complete resolution (defined as improved to baseline with completion of corticosteroids) occurred in 50% of patients [72]. Immune-mediated nephritis has not been well described with pembrolizumab therapy.

12.13 Other Toxicities

IrAEs can occur in any organ system with rarity. Immune-related pancreatitis leading to pancreatic insufficiency and diabetes mellitus has been reported [59, 107]. In general, it is not recommended to obtain baseline or serial amylase and lipase levels unless the patient is symptomatic. Asymptomatic elevations in amylase and lipase occur and do not necessitate treatment or cessation of ICI. Myocarditis and cardiomyopathy from takotsubo-like syndrome have been reported [108, 109].

12.14 Immune-Related Adverse Events and Outcomes

An association between the occurrence of irAEs and favorable response to ICI has been described [34]. For example, in one study, development of irAEs was linked with increased probability of achieving an objective response, and higher-grade irAEs were associated with deeper and more durable responses [105]. Cutaneous irAEs in particular have been associated with improved outcomes. In a large meta-analysis of several melanoma immunotherapies, vitiligo was associated with improved overall survival, better progression-free survival, reduction in risk of disease progression, and reduction in risk of death [34]. A retrospective cohort study also showed a progression-free survival benefit among melanoma, lung cancer, prostate cancer, and Merkel cell carcinoma patients treated with pembrolizumab who developed cutaneous irAEs, compared to patients with no cutaneous toxicity [36]. Notably, the connection between irAE and response to ICI is not completely defined, as other retrospective series have not shown improved overall survival or

time to treatment failure in patients treated with checkpoint inhibitors that develop irAE, compared to patients without immune toxicity [62]. It is important to emphasize that the use of glucocorticoids for treatment of irAEs does not seem to negatively impact outcomes and treatment should not be withheld for this purpose [62].

12.15 Supportive Management During Glucocorticoid Therapy

The management of many irAEs requires prolonged use of steroids leaving patients at risk for opportunistic infections including *Pneumocystis jiroveci*. Prophylactic dosing of TMP/SMX, atovaquone, or pentamidine should be considered in patients treated with 20 mg of prednisone equivalent daily for at least 4 weeks, based on the National Comprehensive Cancer Network guidelines for the Prevention and Treatment of Cancer-Related Infections (Category 2B recommendation). Glucose should also be monitored carefully while on glucocorticoid therapy for steroid mediated hyperglycemia.

12.16 Summary

Immune checkpoint inhibition (ICI) is a new paradigm of targeted cancer therapeutics leading to meaningful outcomes in many diverse malignancies. Inhibitors of cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) and programmed cell death-1 (PD-1) have shown clinically significant antitumor responses leading to approval in advanced melanoma, non-small cell lung cancer, Hodgkin's lymphoma, head and neck, urothelial carcinoma, and renal cell carcinoma, with promising activity in many other tumor types. Though ICI is often well tolerated, a unique array of toxicities termed immune-related adverse events (irAEs) has been identified, which have the potential to be severe or even life-threatening in some patients. IrAEs are T-cell mediated and autoimmune in nature, challenging the oncologist to recognize and treat a new toxicity profile. IrAEs are reported in every organ system but most commonly affect the skin, liver, gastrointestinal tract, and endocrine system. There is currently no way to predict or prevent irAEs. Prompt recognition and management with supportive measures and/or immunosuppression is pivotal, often resulting in reversibility. The use of immunosuppression to treat irAEs has not been found to negatively impact outcomes.

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Preservation of Fertility in the Cancer Patient

13

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Abstract

Preservation of fertility is a key determinant of long-term quality of life of adolescents and young adults treated for curable forms of cancer. The risk of developing primary or secondary infertility after completion of their treatment is variable and difficult to predict. Moreover, evaluation of the extent and reversibility of gonadotoxicity of cancer therapies is currently imperfect, especially in young women.

The term oncofertility was originally coined to describe a new discipline that bridges oncology and reproductive medicine to discover and apply new fertility preservation (FP) options for young patients with cancer. Although there is a great interest in this field, due to the lack of large prospective cohort studies and randomized trials, the level of evidence is higher than III for most of the recommendations.

The most established methods of preserving fertility are sperm banking in men and embryo/oocyte cryopreservation in young women. However, many alternative options, though still experimental, are in development that can already be proposed to young patients in well-defined conditions.

Despite the progress and refinement of FP techniques and the increase in educational resources, an information gap between patients and healthcare teams still persists. Concerted efforts must be made in parallel and global oncofertility programs developed to offer high-quality techniques to meet this unique need in young patients with cancer.

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M. A. Dicato, E. Van Cutsem (eds.), *Side Effects of Medical Cancer Therapy*,
https://doi.org/10.1007/978-3-319-70253-7_13

Keywords
Fertility preservation · Quality of life · Information · Communication · Reproductive medicine · Methods of medically assisted procreation

13.1 Introduction

As the curability of most cancer subtypes in children and young adults has improved, preservation of an optimal quality of life has become a major issue and requires from oncologists an increasing acknowledgment and prevention of long-term adverse effects of their treatments. Among these, the loss of reproductive potential of cancer survivors has major repercussions on their quality of life [1–4]. It is often reported by young women treated for breast cancer as one of the most devastating experiences, even more stressful than the diagnosis of cancer itself [5].

Approximately 5–6% of cancer patients are younger than 40 years, and a large proportion of them have not completed their parenthood. About 50% of current oncologic treatments may have severe repercussions on their reproductive potential. Fertility items and potential fertility preservation modalities are challenging in young patients although much less complex in men than in women.

13.2 Fertility Preservation in Men

13.2.1 Risk Factors for Infertility

Cancer itself can be correlated with azoospermia in conditions like Hodgkin's disease and testicular cancer. However, no correlation between semen alteration and cancer stage or associated symptoms has been detected. Several surgical procedures (like pelvic surgery for testicular or prostate cancer) can cause severe damage, interfering with ejaculation. However, the primary threat for fertility in men is compromised sperm production, quality and mobility, and DNA damage secondary to chemotherapy and/or radiotherapy exposure (Table 13.1).

If permanent infertility can result from quantitative and qualitative damage to spermatogenesis stem cells, more frequently, temporary impairment of spermatogenesis occurs with most cytotoxic agents, up to 2 years after completion of therapy. As in women, the extent of damage to gametogenesis depends on the age of the patient and on the type, the cumulative dose, and the schedule of chemotherapy. A large proportion of treated patients maintains or regains organ level of spermatogenesis adequate to obtain spontaneous conception.

Radiotherapy, even at low dose, is toxic for developing sperm tissue; the delivery of high-dose pelvic irradiation (as required for prostate and rectal cancer or testicular seminoma) can induce permanent damage to testicular function and also possibly some level of erectile dysfunction.

Table 13.1 Risk of azoospermia according to treatment regimen

Major (*prolonged or definitive azoospermia*):
Total body irradiation
Testicular irradiation at a dose $\geq$2.5 Gy
High-dose alkylating agents ± radiotherapy for transplant conditioning
Cyclophosphamide >7.5 g/m^2 (cumulative dose)
Cranial brain radiation ($\geq$40 Gy)
Intermediate (*prolonged azoospermia*):
Uncommon at standard dose (BEP regimen for 2–4 cycles)
Cumulative cisplatin dose <400 mg/m^2 or carboplatin <2 g/m^2
Low risk (*temporary azoospermia*): Nonalkylating chemotherapy (ABVD)
Unknown: Irinotecan, oxaliplatin, bevacizumab, cetuximab, erlotinib, etc.

13.2.2 Options to Preserve Fertility in Men

13.2.2.1 Sperm Banking

The best option for FP in males is cryopreservation of semen before treatment, which is easily accessible and widely available (in more than 95% of young male cancer patients) [6]. Collection of three or four samples after an approximately 48-h period of abstinence between sampling (a total of more than 5 days) is ideal. Long-term follow-up studies of cryopreservation (up to 28 years) suggest a very prolonged conservability of sperm capacity for fertilization. The significance of notifying the patient of potential risk (even if minimal) of iatrogenic infertility as early as possible remains critical. It is strongly advisable to complete sperm banking before starting therapy to avoid increased genetic damage in sperm collected after the start of therapy.

Limitations to this intervention include the inability to masturbate and/or ejaculate as a result of age, discomfort, or level of illness. In these rare situations, some alternative, though more invasive, procedures can be offered, such as electroejaculation under general anesthesia or microsurgical epididymal sperm aspiration.

13.2.2.2 Alternative Options

Cryopreservation of spermatogonial stem cells and testicular tissue is an outpatient procedure that can be considered for prepubescent boys or when sperm banking is impossible for any other reason. As for ovarian cortex cryopreservation in females, this method is still experimental (with no live births reported to date) and carries a theoretical risk of contamination of testicular tissue by cancer cells.

The use of gonadal shielding during radiotherapy to reduce the dose of radiation delivered to the testis can be offered when feasible (eventually in combination with sperm banking).

In cancer survivors who had not their semen cryopreserved before cytotoxic therapy and had sustained azoospermia, successful treatment via the use of microsurgical testicular sperm extraction has been recently reported in a large US experience [7].

Of note, paucity of data is available on fatherhood after cancer, but most of published data are reassuring: the risk of birth defects does not seem to increase at least if a delay of more than 2 years between paternal cancer diagnosis and conception is respected [8].

13.3 Fertility Preservation in Women

The issue of FP is much more complex in young women than in men because simple, rapid, and validated procedures like sperm banking are not available: the percentage of women who choose to undergo the available FP options after counseling varies from 2 to 50% [9]. Moreover, reliable methods to predict and evaluate accurately the gonadal toxicity of treatments in females are still lacking.

13.3.1 Risk Factors and Evaluation of Gonadal Repercussions of Treatment

If the diagnosis of cancer itself does not seem to affect female fertility, most anticancer treatments can induce a variety of reproductive disorders, including immediate, definitive infertility, premature menopause, and compromised ability to carry a pregnancy due to uterine damage. The evaluation of risk of gonadotoxicity is hampered by several factors. First, long-term follow-up studies of reproductive function in female survivors are lacking, precluding the distinction between acute and permanent ovarian failure. Moreover, the assessment of secondary ovarian failure relies mostly on clinical parameters like the rate of prolonged chemotherapy-induced amenorrhea (CIA) rather than on objective indicators of ovarian reserve such as ultrasonic parameters (antral follicle counts or AFCs) or serum hormonal levels [10, 11]. More recent papers report on the value of anti-Müllerian hormone (AMH) assessment as a reliable predictor of primary follicle reserve before, during, and after chemotherapy, preferable in that setting to any other conventional dosage (estradiol, follicle-stimulating hormone [FSH], and inhibin B): iterative measurements of serum AMH levels enable quantitative evaluation of ovarian damage caused by toxic interventions (chemo- and radiotherapy) and are becoming indispensable to access ovarian reserve patients who desire to preserve fertility [12].

The risk of secondary ovarian failure depends greatly on the age of the treated patient, on her pretreatment fertility status, and on the type and dose of chemotherapy (high dose of alkylating agents being the more toxic). Definitive infertility can also result from abdominal and/or pelvic radiotherapy (according to doses and fields of irradiation) and obviously from most forms of nonconservative gynecologic surgery.

Table 13.2 Risk of prolonged CIA in women

Degree of risk	Treatment protocol
High (>80% CIA)	Whole abdominal or pelvic irradiation (≥6 Gy in adults)
	Total body irradiation
	Cyclophosphamide ≥ 5 g/m² in women >40
	Any high cumulative dose of alkylating agent
	Cranial radiation ≥ 40 Gy
Intermediate (30–70% CIA)	CMF, CEF, or CAF × 6 in women aged 30–39 (breast cancer)
	AC in women >40 (breast cancer)
	BEACOPP in women <40 (Hodgkin's disease)
Low risk (<20% CIA)	AC in women aged 30–39 (breast cancer)
	CMF, CEF, or CAF in women <30
	Nonalkylating chemotherapy (ABVD)
Unknown	Taxanes
	Oxaliplatin
	Irinotecan
	Targeted therapies (bevacizumab, cetuximab, trastuzumab, erlotinib, imatinib, etc.)

If the effects of cytotoxic regimens depend partly on the baseline ovarian reserve, they become particularly pronounced by the time the patients reach 40 years of age. As young women have a large primordial follicle pool, they are less likely to lose all their reserves immediately after chemotherapy, but even those women who resume regular menses after treatment will eventually experience premature ovarian failure as a consequence of a significant loss of primary follicles.

Taken together, all these variables make any accurate prediction or evaluation of the incidence and reversibility of iatrogenic infertility difficult at an individual level. Table 13.2 reports grossly on the rate of prolonged CIA during and after treatment, which is the only available (but quite imperfect) surrogate measure of impact on female fertility. However, these data are even lacking for many modern treatments already used in the routine.

13.3.2 Options to Preserve Fertility in Women

Currently, the options for FP in female patients undergoing chemotherapy are limited; most are still investigational, and highly variable success rates are reported. The potential benefits and drawbacks of the four main FP methods in young women are summarized in Table 13.3.

13.3.2.1 In Vitro Fertilization or Oocyte Preservation

In vitro fertilization (IVF) and embryo banking are the best established forms of FP with excellent chances of future pregnancy (with a success rate per embryo transfer of 15–45%). More recently, oocyte cryopreservation has become a standard strategy for FP in single women who are not interested in using donor sperm, but, similarly

Table 13.3 Techniques of FP in young women

Options	Benefits	Concerns
1. IVF and embryo cryopreservation	Well-established technique	Requires a male partner
	Clinical availability	Ovarian stimulation
		Delay
2. Oocyte cryopreservation	No male partner required	Efficacy unknown
		Ovarian stimulation
		Delay
3. Cryopreservation of ovarian tissue	No male partner required	Pregnancy rate unknown
	No ovarian stimulation	Potential malignant tissue grafting
	No delay	Laparoscopy
4. Ovarian suppression by LH–RH analogues	No male partner required	Unproven efficacy
	Noninvasive technique	Safety concerns
	No delay	

to IVF, it requires an ovarian hyperstimulation followed by oocyte retrieval and entails a delay in treatment ranging from 2 to 6 weeks [13, 14].

Any controlled ovarian stimulation (OS) protocol raises two potential safety issues of concerns: delay in cancer treatment initiation and possible negative impact of OS on the prognosis of patients with hormone—sensitive tumors (mostly breast cancers).

A single cycle of OS can take up to 6 weeks from the first day of the menstrual cycle to complete: this includes a sequence of hormonal injections during 10–12 days to stimulate egg development and oocyte retrieval after a close monitoring of growth. In practice, it entails a delay in onset of cancer treatment that sometimes exceeds 2 months (e.g., if more than one cycle of IVF is needed): However, this can be significantly shortened by early referral of potential candidates to reproductive specialists. For this reason, some authors suggest a global implication and awareness of multidisciplinary teams caring for young patients (like breast units) and a real shift in responsibilities. In the case of young breast cancer patients, a rapid referral of potential young candidates for FP techniques from surgeons and even from radiologists (instead of medical oncologists) to specialists in reproductive medicine could shorten this delay by 2–6 weeks. Another emerging approach to attempt to limit this delay is an emergency OS at a random cycle date without waiting for the spontaneous cycle to start [15].

A second barrier to adopt IVF or oocyte preservation as a routine procedure of FP in breast cancer patients is the concern about estradiol peak (sometimes 30 times above baseline values) secondary to ovarian stimulation. Several alternative regimens of OS can be proposed in that setting like protocols incorporating letrozole or tamoxifen [16]. To completely avoid the need of OS, cryopreservation of immature oocytes or oocytes matured in vitro is under clinical development. All these strategies have to be considered as experimental. Up to now, preliminary data suggest comparable outcomes (recurrence of breast cancer and survival rate) in young

Table 13.4 Summary of FP procedures: an algorithm

Evaluation of risk of gonadotoxicity		
Discussion with the patient		
Interest and feasibility of FP techniques		
Validated techniques		*Experimental techniques*
Males	Females	Cryopreservation of ovarian/ testicular tissue
Sperm banking	Cryopreservation of embryos/oocytes	
	Gonadal shielding	Ovarian suppression by LH-RH analogues
	Oophoropexy	

Adapted from [13, 14]

women stimulated with this IVF regimen and a control group of unstimulated patients [17, 18].

From a technical perspective, if embryo and oocyte cryopreservation have become standard options for FP, two different methods for cryopreservations are currently available: slow freezing and vitrification but the latter (vitrification) showed better performance in recent studies (Table 13.4).

13.3.2.2 Cryopreservation of Ovarian Tissue

Surgical excision of ovarian cortex tissue and cryopreservation of dissected slices have emerged as an innovative, promising, though still experimental, option for female FP [19]. The theoretical advantages include the rapidity of this laparoscopic procedure, which can provide a large number of follicles and oocytes at any time during the menstrual cycle without any previous OS. However the best candidates for ovarian tissue cryopreservation are prepubertal girls (the only option in this population).

Another promising indication is the situation in which patient has already received chemotherapy (a substantial number of follicles remaining present in cortical tissue).

The ovarian tissue can be used for orthotopic transplantation, with a possibility to restore both endocrine function and egg production for spontaneous pregnancy but also for in vitro growth and maturation of oocytes as emerging options in the future [9, 20].

However, the success rate of this attractive procedure is unknown; to date, a total of 40 live births have been reported after orthotopic transplantation of thawed ovarian tissue [21].

Moreover, despite screening for tumor cells before freezing and again before reimplantation with appropriate histologic, immunologic, and molecular biology techniques, the risk of viable malignant cell contamination and restoration persists. This risk could be higher in leukemia patients than in patients with Hodgkin's lymphoma or breast cancer [22, 23].

Very active research tracks are ongoing in this domain, aimed at optimizing the efficacy and safety of the procedure. Examples include avoidance of ischemic injury

(transplantation of whole cryopreserved ovary), isolated follicle transplant, in vitro follicular culture, pharmacological protection of oocytes, and new freezing-thawing techniques.

13.3.2.3 Ovarian Suppression by LH–RH Analogues

During the last two decades, animal studies and small observational series have suggested that LH–RH agonists, given together with chemotherapy, might offer protection against premature ovarian failure; however, no consistent explanation nor biologic plausibility can be hypothesized, FSH receptors being exclusively expressed on follicles during advanced stages of development. Speculative mechanisms of action include the reduction of blood flow to the ovaries.

This pharmacologic approach is an attractive option to preserve gonadal function and fertility given the wide availability of such agents and the advantage of avoiding any delay in the initiation of anticancer therapy: monthly LH–RH injections (triptorelin or goserelin) have to begin at least 2 weeks prior to the first cycle of chemotherapy; this time is required to obtain hormonal suppression after an initial stimulatory "flare." During this period of ovarian overactivity, the ovary would be placed at particular risk from the toxic effect of chemotherapy.

A total of ten randomized studies in breast cancer patients [24–26] and two in lymphoma patients [27, 28] have been reported to evaluate this strategy relying mostly on incidence and duration of CIA as surrogate for infertility. Overall, the results are conflicting especially when reliable indicators of ovarian reserve (like AMH levels or AFC at ultrasound) are evaluated: the conclusions of a recent meta-analysis conducted in breast cancer patients suggest a potential efficacy of this strategy in reducing the risk of premature ovarian failure [26]; in contrast, the long-term results in lymphoma patient are more discussable [28].

In the real world, ovarian suppression with LH–RH before and during chemotherapy can be considered as reliable strategy for FP (at least in breast cancer patient) but should not be presented as equivalent to standard options which are embryo or oocyte cryopreservation.

13.3.2.4 Other Options of FP in Females

Adapted surgical and/or radiotherapy procedures can be offered in selected cases of pelvic or abdominal tumors:

Ovarian transposition (or oophoropexy): this intervention can be done by laparoscopy and allows the displacement of ovaries as far as possible from the radiation fields, though scatter radiation and alteration of ovarian blood supply can be reasons behind ovarian failure.

Gonadal shielding during radiation therapy:

Conservative gynecologic surgery, like trachelectomy in early cervical cancer, limited surgical staging for borderline or early invasive ovarian cancer and even in early-stage endometrial cancer. These surgical approaches can be considered in very selected cases and after careful multidisciplinary discussion.

Donor embryos, donor eggs, gestational surrogacy, and adoption are other potential options subject to national bioethics. Nevertheless, some evidence suggests that cancer survivors prefer biologic offspring over adoption and third-party reproduction opportunities and are rather interested in protecting their own reproductive capacity [2].

13.4 Attitudes Toward FP in Cancer Patients

When questioned specifically on this issue, most young cancer patients manifest a huge interest in FP questions, as they present a positive perspective for the future; however, these issues are still suboptimally approached by oncologists in daily practice, despite international guideline recommendations like the ASCO and ESMO guidelines [13, 14]. Retrospective series report a consistent proportion of 30–60% of oncologists appropriately tackling these issues before treatment, even in male patients despite the wide and rapid accessibility to sperm banking [1–3, 9, 29].

The most apparent barriers to communicate in that field are as follows:

- Lack of physicians' knowledge about real risks of infertility from their treatments, about FP techniques, and about inherent risks (mainly delay and stimulation of hormone-responsive tumors)
- Lack of appropriate collaboration with a team of fertility specialists
- Lack of time to discuss this issue and wrong appreciation of patient's interest for FP procedures according to her/his parenting or marital status
- Anticipation of patient's wish to begin the treatment rapidly and to give priority to optimal chances of cure

The topic of FP may be understated when it is presented by oncologists along with a myriad of other potential, sometimes severe, adverse effects; additional educational materials (booklets, website, etc.) may be required to help facilitate conversation and decision-making [30].

Moreover, pretreatment fertility and FP counseling delivered not exclusively by an oncologist but also by a fertility specialist significantly improve long-term quality of life in reproductive-age women with cancer [31]; this issue has been evaluated by validated quality-of-life scales (like the decision regret score), but most potential candidates, sometimes under pressure from their families or their physicians, believe they have no time to pursue such consultation.

In parallel to technical and practical aspects, two major issues must be pointed out by oncologists early enough in the complex discussion about FP:

- It is mostly recommended to female patients to wait 2–5 years after cancer treatment completion before trying to achieve spontaneous or medically assisted pregnancy. Recent data seem very reassuring about the outcome of breast cancer survivors who became pregnant even earlier after their treatment [32], and this

remains true for the hormone-responsive subset of patients [33]. They could even have a lower risk of death compared to patients who did not become pregnant, though selection bias partly could contribute to this decreased risk ("healthy mother effect").

- There is currently no evidence that a history of cancer, cancer treatment, or fertility intervention increases the rate of congenital abnormalities or of cancer in the progeny compared to general population; the risk of miscarriage and of preterm delivery can be a concern, but it is limited to a small fraction of women who had radiation to their pelvic area or some fertility-sparing surgery.

Finally, as the FP decisions are made in the context of a life-changing and potentially life-threatening diagnosis, the broader application of FP techniques to young cancer patients will undoubtedly raise new difficult ethical and legal problems in the future (like ownership of embryos after death of one partner, preimplantation genetic diagnosis in conjunction with IVF, reimplantation of embryos in oligometastatic setting). It could require an adaptation of bioethical legislation to this specific population [34]. These problems are beyond the scope of this chapter.

Conclusions

Young patients confronted with a diagnosis of cancer have unmet needs for information about the potential risks of infertility and available options of FP. Although options (at least for young women) are still limited, advances in both gamete and gonadal tissue cryopreservation as well as assisted reproductive technologies are quickly developing. Oncofertility has emerged as a new hybrid specialty, requiring cross-disciplinary—disciplinary directions and implying from all oncologists minimal basic knowledge, communication skills, and effective collaboration with fertility specialists, as emergency decisions and measures have to be taken before any cytotoxic treatment. Basic information delivered by oncology teams to their young patients can be relayed by educational materials, but, more importantly, the potential candidates must be rapidly referred to reproductive medicine specialists for optimal individualized management.

On the other hand, young patients must be made aware of the limitations of the currently available FP techniques in order to establish reasonable expectations; sperm banking and embryo-oocyte cryopreservation are actually considered the only standard procedures. Other strategies (pharmacological protection of the gonads and gonadal tissue preservation) while promising are still experimental and must be proposed as such. Patients must be informed of persisting uncertainties in up-to-date knowledge about potential repercussions of modern therapies on their fertility, success rate of different procedures, and possible additional risks from available options. However, a multidisciplinary approach that integrates both realism and medical progress should facilitate a meaningful discussion that assists young patients in making the parenthood decisions that are right for them.

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Cardiotoxicity

14

I. Brana, E. Zamora, G. Oristrell, and J. Tabernero

Abstract

While outcomes in cancer patients have dramatically improved with the development of novel cancer chemotherapies and combination treatment, this is nonetheless associated with emerging concerns over drug-induced cardiotoxicity. Moreover, the recent incorporation of targeted therapies into therapeutic regimens has widened the cardiotoxic spectrum. Awareness of anticancer drug-induced cardiotoxicity is essential for adequate patient monitoring and early cardiotoxicity detection and treatment. This rising concern is also reflected in drug development, as efforts have been made to improve the characterization of potential cardiotoxicity of new compounds during the early phases of development and to design safer drugs. This chapter summarizes the major cardiotoxic effects and pathophysiology of a large number of antineoplastic treatments currently in use. Existing recommendations for early treatment and future development are also described.

Keywords

Cardiotoxicity · Side effect · Left ventricular dysfunction · Heart failure · Angina Arrhythmia · QTc interval

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M. A. Dicato, E. Van Cutsem (eds.), *Side Effects of Medical Cancer Therapy*,
https://doi.org/10.1007/978-3-319-70253-7_14

14.1 Introduction

Oncologists are becoming increasingly concerned at the presence of cardiotoxicity associated with many antineoplastic agents currently used to effectively treat patients, particularly in light of the observation that such chronic adverse events may worsen survivor long-term outcome [1–4]. This concern is even more relevant as population is aging, and both cancer and cardiovascular diseases are common in this elderly population, and the presence of an underlying heart condition increases the risk of cardiotoxicity [5]. In addition, novel mechanisms of cardiotoxicity have been described with both classic cytotoxics and new targeted therapies. Hence, there is a special need for cooperation between cardiologists and oncologists to improve cancer-associated cardiovascular event prevention and management. These needs have been crystallized into the creation of the novel discipline dedicated to study the cardiovascular issues of cancer patients: cardio-oncology or onco-cardiology [6].

Cardiotoxicity is defined by the National Cancer Institute (NCI) as "toxicity that affects the heart" [6], which not only includes direct effects on the heart but also hemodynamic flow alterations or thrombotic events associated with cancer treatment. The most common complications related to anticancer treatment include dilated cardiomyopathy due to myocardial necrosis, rhythm disturbances, and angina or myocardial infarction secondary to vaso-occlusion or vasospasm. Although anticancer drugs may induce cardiotoxicity through a several mechanism, this chapter will focus on the predominant mechanism for each drug.

14.2 Cardiomyopathy: Left Ventricular Dysfunction

Anthracycline-related cardiomyopathy is the paradigm of chemotherapy-induced cardiotoxicity, but, in recent years, other agents have also been shown to induce cardiomyopathy, such as trastuzumab, pertuzumab, and different tyrosine kinase inhibitors such as sunitinib, lapatinib, and imatinib. Anticancer drugs inducing cardiomyopathy have been classified into two classes according to the reversibility and pathophysiology of the toxicity [7] (Table 14.1). Type I agents, such as anthracyclines, mitoxantrone, or cyclophosphamide, induce irreversible myocardial damage

Table 14.1 Drug-induced ventricular dysfunction classification

	Type I	Type II
Reversibility	No	Yes
Cumulative dose related	Yes	No
Ultrastructural changes	Vacuoles, sarcomere disruption, necrosis	Not relevant
Drugs	Doxorubicin Mitoxantrone Cyclophosphamide	Trastuzumab Sunitinib Lapatinib Imatinib Bortezomib

which correlates with the cumulative dose, while type II agents, such as trastuzumab or tyrosine kinase inhibitors (TKIs), induce potentially reversible cardiomyopathy without ultrastructural myocyte damage. Based on the transient nature of type II agent-induced cardiotoxicity, these agents may be resumed after toxicity recovery, assuming an acceptable benefit-risk.

14.2.1 Anthracyclines

Anthracyclines, the backbone of breast cancer, sarcoma, and hematological malignancies treatment, can potentially induce cardiotoxicity either as an acute/subacute event or as a chronic side effect [5, 8–10]. Acute/subacute complications occur within the first 2 weeks of dosing and include a variety of uncommon events such as electrocardiographic abnormalities, supraventricular or ventricular arrhythmias [11], or a pericarditis-myocarditis syndrome [12]. Chronic cardiotoxicity is a dose-limiting side effect of anthracyclines characterized either by an asymptomatic decline in myocardial function or by clinical heart failure. In some patients, chronic cardiotoxicity appears within the first year after treatment completion, while in other patients, this toxicity occurs as a later side effect [13]. A meta-analysis including eight randomized controlled trials concluded that patients receiving anthracyclines have higher risk of cardiotoxicity compared to patients who do not receive anthracyclines (odds ratio (OR) 5.43) [14]. Higher cumulative doses (>300 mg/m^2 of doxorubicin) are associated with higher cardiotoxicity incidence [5, 15]. Other risk factors include prior cardiac irradiation [16], previous heart disease [17], hypertension [17], coronary artery disease [17], and age >65 years [18]. According to the presence of these risk factors, patients can be stratified into three risk categories: low-risk (no risk factors), moderate-risk (1–2 risk factors), and high-risk (>2 risk factors) categories [5]. In addition to these risk factors, patients might be more prone to anthracycline-induced toxicity due to their inherited background. The presence of certain germline polymorphisms in genes such as hyaluronan synthase 3 (HAS3) seems to be associated to increased risk of anthracycline toxicity through decreased protection from reactive oxygen species (ROS)-mediated injury [19].

Several mechanisms have been implicated in anthracycline-related cardiotoxicity. The main mechanisms include oxidative stress—in which free radicals induce cellular damage through lipid peroxidation [6]—and cardiomyocyte DNA damage through topoisomerase II blockade. Other potential mechanisms include mitochondrial DNA mutations, calcium imbalance, direct DNA damage, and deregulation of cardiac transcription factors [20]. Pathological findings of anthracycline-induced myocardial include vacuole formation, disarray of the contractile elements, and myocyte necrosis [21–23]. The intensity of the damage correlates with both dose [8] and rate of infusion, being higher rates of infusion those more cardiotoxic [18, 24].

Several approaches have been proposed to prevent and minimize anthracycline-induced cardiotoxicity involving cardiologist evaluation prior treatment initiation, the use of less cardiotoxic anthracycline compounds, or the addition of co-adjuvant treatments. Cardiologist evaluation prior to anthracycline treatment includes the

evaluation of the abovementioned risk factors associated to anthracycline toxicity, the adequate correction of those risk factors potentially reversible, and the subsequent close monitoring of high-risk patients. In the last decades, newer anthracycline compounds, such as epirubicin, or novel formulation, such as liposomal anthracyclines, have been developed to reduce cardiotoxic effects. Epirubicin is a semisynthetic epimer of doxorubicin which induces less cardiotoxicity than doxorubicin at equivalent myelosuppressive doses, allowing administration of approximately one-third more equivalent treatment cycles [25–28]. Liposomal formulations confer substantial cardioprotection, as they induce changes in the drug distribution pattern, achieving lower concentrations in the heart and higher concentrations in the tumor. Hence, pegylated liposomal doxorubicin allows administration of twice as many cycles compared to the native compound and constitutes an alternative in patients requiring anthracycline treatment when a cardiac-sparing agent is sought [29, 30]. Other possible approach to decrease the risk of cardiotoxicity is the use of an adjunctive treatment such as beta-adrenergic blockers or dexrazoxane. Regarding dexrazoxane, the concerns regarding a possible increased risk of secondary malignancies and a potential decrease in antitumor efficacy have made the FDA and the American Society of Clinical Oncology (ASCO) recommend dexrazoxane in the metastatic context only for patients who are planning to receive cumulative doses of doxorubicin exceeding 300 mg/m^2 [31].

14.2.2 Mitoxantrone

Structurally related to anthracyclines, mitoxantrone induces similar ultrastructural changes in myocytes. Its potential to induce cardiotoxicity is linked to its cumulative dose or the cumulative dose of any other type I agents previously received [32].

14.2.3 Cyclophosphamide

This alkylating agent produces myocardial hemorrhagic necrosis, especially with high-dose regimens. In contrast to anthracyclines and mitoxantrone, cyclophosphamide-induced cardiotoxicity does not seem to be related to the cumulative dose but to the individual dose administered in an individual cycle; hence, patients receiving high-dose cyclophosphamide are at higher risk [33, 34].

14.2.4 Trastuzumab

This humanized monoclonal antibody against HER2 tyrosine kinase receptor is effective in patients with HER2-positive breast cancers (20–25% of all breast cancers). Trastuzumab is the archetype of type II cardiotoxic agent: its toxicity is not dose-dependent; it does not induce ultrastructural changes in the cardiomyocyte, and it is reversible [35]. Hence, rechallenge may be often tolerated after

cardiotoxicity recovery. Trastuzumab induces left ventricular dysfunction which mimics the stunning or hibernation phenomenon described in myocardial ischemia [7]. Extensive data have been published supporting the underlying mechanism for this toxicity: HER2 is constitutively expressed in the heart, and preclinical studies suggest that perturbation of downstream pathways affects cardiomyocyte survival and adaptation to stress [36, 37]. In addition, anthracycline administration induces HER2 overexpression, which may increase the trastuzumab-induced cardiotoxicity if administered simultaneously or shortly after anthracyclines [38].

A number of risk factors have been associated with higher incidence of trastuzumab-induced cardiotoxicity: age > 50 years, borderline left ventricular ejection fraction (LVEF) prior to trastuzumab treatment, history of cardiovascular disease, cardiovascular risk factors (diabetes, dyslipidemia, or body mass index >30), treatment sequence when administered with chemotherapy, and prior or simultaneous administration with other chemotherapeutic agents, especially with anthracyclines [9, 35, 36, 39–42]. The incidence of LVEF decrease or asymptomatic heart failure with single-agent trastuzumab was 7% in both metastatic and adjuvant setting [42, 43]. When administered concomitant with paclitaxel, the incidence of symptomatic heart failure or asymptomatic LVEF decrease ranged 13–18% [42, 44], but when administered with anthracyclines, the incidence rose to 27%. Prior treatment with anthracyclines is a relevant risk, especially if total doxorubicin cumulative dose exceeds 300 mg/m^2 [39]. To further characterize the role of prior anthracyclines, the Breast Cancer International Research Group performed the BCIRG-006 assessing the efficacy and safety of trastuzumab combined with a non-anthracycline regimen (docetaxel, carboplatin, and trastuzumab) compared to trastuzumab combined with docetaxel administered sequentially to an anthracycline-containing regimen (four cycles of doxorubicin and cyclophosphamide, followed by four cycles of docetaxel and trastuzumab), and compared to an anthracycline-containing regimen without trastuzumab [45]. In this trial, the risk of developing New York Heart Association (NYHA) class III or IV heart failure was significantly lower in the non-anthracycline arm (0.38%) versus the anthracycline-containing arm (1.96%). Two scores have been developed to predict the risk of trastuzumab-induced cardiotoxicity: one using the data from the NSABP B-31 trial and other using the data from the Surveillance, Epidemiology, and End Results (SEER)/Medicare Database. The first score includes age and baseline LVEF to predict the absolute risk of heart failure in individual patients [44], and the second score predicts 3-year risk of heart failure or cardiomyopathy after trastuzumab [46]. Nonetheless, these scores need independent validation before to be considered for use in general practice.

14.2.5 Lapatinib

Lapatinib is an oral dual inhibitor of the epidermal growth factor receptor and of HER2 which may have a more favorable cardiac safety profile than trastuzumab. Pooled data from 44 studies suggest that 1.6% of patients treated with lapatinib

developed clinical failure or experienced an absolute LVEF decrease of ≥20% [47]. In most cases cardiac events were reversible. The mechanism of toxicity is related to impaired myocyte response following injury secondary to inhibition of HER2 downstream pathways [36, 37]. However, the reason why lapatinib and trastuzumab induce cardiotoxicity at different rates remains controversial.

14.2.6 Ado-Trastuzumab Emtansine (T-DM1)

Ado-trastuzumab emtansine (T-DM1) is an antibody-drug conjugate composed of trastuzumab, a thioether linker, and maytansine, an antimitotic agent. In a phase III study comparing T-DM1 versus capecitabine plus lapatinib in patients with metastatic breast cancer previously treated with taxane and trastuzumab, T-DM1 induced left ventricular dysfunction in 1.7% of patients, while 1.6% experienced left ventricular dysfunction in the control arm. Left ventricular dysfunction was defined as LVEF <50% or a decrease in 15% from the baseline. Only one patient treated with T-DM1 in this study developed grade 3 symptomatic left ventricular systolic dysfunction [48]. The FDA prescribing information recommends LVEF assessment prior treatment start and every 3 months during treatment with T-DM1 [49].

14.2.7 Pertuzumab

Pertuzumab is a monoclonal antibody that binds to epitope II of the HER2 and prevents HER2 homo- and heterodimerization with other HER-family receptors. The data from both phase II and phase III trials (CLEOPATRA) confirmed that the addition of pertuzumab to trastuzumab was not associated with increased cardiotoxicity [50, 51]. Pertuzumab is approved in combination with trastuzumab in the metastatic and in the adjuvant setting. The FDA-approved prescribing information for pertuzumab recommends LVEF assessment prior treatment start and regular monitoring during treatment: every 6 weeks in the adjuvant setting and every 3 months in the metastatic setting [52].

14.2.8 Other Kinase Inhibitors

In addition to anthracyclines and targeted therapies directed to HER2, different approved kinase inhibitors may produce left ventricular dysfunction to some extent (Table 14.2) [53]. Toxicity can range from asymptomatic LVEF decrease to severe heart failure. Predisposing factors of left ventricular dysfunction related to kinase inhibitors include prior anthracycline therapy and TKI-induced hypertension. Kinase inhibitors belong to type II cardiotoxic agents; hence, their toxicity is usually reversible upon withholding drug and instituting medical management. Upon recovery, patients are candidates to treatment rechallenge. The interval until left ventricular onset is poorly characterized; hence, baseline and on-treatment periodic LVEF assessment is recommended [53].

Table 14.2 Tyrosine kinase inhibitors related to left ventricular dysfunction

Drug	
Afatinib	Nilotinib
Bortezomib	Pazopanib
Bosutinib	Ponatinib
Dabrafenib	Sorafenib
Dasatinib	Sunitinib
Lapatinib	Trametinib
Lenvatinib	Vandetanib

14.2.8.1 Sunitinib

Sunitinib is an oral inhibitor of vascular endothelial growth factor receptor (VEGFR) 1–3, platelet-derived growth factor receptor (PDGFR)-α and -β, KIT, fms-related tyrosine, up-to-date kinase 3 (FLT3), colony-stimulating factor 1 receptor (CSFIR), and rearranged during transfection (RET). Chu et al. retrospectively analyzed the cardiotoxicity of this agent in 75 patients with gastrointestinal stromal tumors enrolled in phase I and II trials using sunitinib. The incidence of LVEF decrease >10% was 28%, while the incidence of heart failure was 8% [54]. LVEF significantly improved after sunitinib discontinuation, and no cumulative dose relationship was observed.

It is thought that this cardiac toxicity is related to an "off-target" effect through ribosomal S6 kinase inhibition, which causes ATP depletion and activates the intrinsic apoptotic pathway [36]. In contrast to trastuzumab-induced cardiomyopathy, sunitinib-induced cardiomyopathy is characterized by the presence of some changes in myocardial biopsies, such as alterations in mitochondria [54]. An additional potential mechanism of toxicity is through simultaneous hypertension induction associated to impaired heart adaptation to pressure overload through VEGFR inhibition [36]. The role of angiotensin-converting enzyme inhibitors or beta-blockers—drugs widely used to treat sunitinib-induced hypertension—on sunitinib-induced left ventricular dysfunction is still unknown [5].

14.2.8.2 Imatinib

Imatinib is a small molecule tyrosine kinase inhibitor of ABL1 (protein encoded by the Abelson murine leukemia viral oncogene homolog 1), ABL-related gene (ARG), platelet-derived growth factor receptors alpha and beta (PDGFR-α and -β), and KIT. Peripheral edema has been described along with a 0.6% incidence of heart failure, usually in older patients with prior cardiovascular disease [55]. This toxicity is considered to be secondary to endoplasmic reticulum stress response activation, and it is mediated by PKR-like ER kinase (PERK) [56].

14.2.8.3 Bortezomib

Bortezomib is a proteasome inhibitor associated with a 5% incidence of heart failure [57]. Proteasome inhibition seems to induce endoplasmic reticulum stress leading ultimately to myocyte dysfunction [9, 58].

14.3 Coronary Artery Disease

In a population-based study, an increased risk of coronary artery disease compared to the general population has been described among patients with certain cancers, such as multiple myeloma and non-Hodgkin lymphoma [59]. Systemic anticancer treatments have shown to induce coronary events, mainly through two different mechanisms: coronary artery vasospasm and arterial thrombotic events. 5-fluoruracil is the most commonly used drug associated with the first mechanism, while antiangiogenic drugs are the archetype of the second. Other chemotherapeutic agents commonly linked to cardiac ischemia include purine analogues, topoisomerase inhibitors such as etoposide, and antitumor antibiotics. Recently, two multi-kinase inhibitors not targeting angiogenesis—nilotinib and dasatinib—have been also associated to an increased risk of artery coronary events [60].

14.3.1 Fluoropyrimidines

Treatment with 5-fluorouracil and capecitabine may lead to cardiac ischemia, myocardial infarction, and malignant ventricular arrhythmia through coronary vasospasm. The incidence of 5-fluoruracil-induced angina varies widely between studies, ranging from 1 to 68% [9, 61–64]; the mean onset is 72 h after treatment initiation [65]. The incidence of capecitabine-induced toxicity ranges from 3 to 9% [9, 62], and its onset occurs 3 h to 4 days after treatment initiation. In a retrospective study including over 600 patients treated with 5-fluoururacil, 4% developed clinical symptoms, electrographic changes, or both [9, 66]. In most cases, patients had a prior coronary condition. Treatment with nitrates and calcium-channel blockers has successfully prevented new episodes of ischemia in these patients [64]. 5-fluouroracil-induced toxicity appears to be dose- and rate-dependent, with continuous infusion and high doses (>800 mg/m^2) being associated with higher rates of toxicity [65].

14.3.2 Antiangiogenic Therapies

One of the proposed mechanisms for antiangiogenic drug-induced arterial thrombosis is mediated by inhibition of the vascular endothelial growth factor (VEGF) which may impair endothelial cell regeneration after incidental trauma, leading to subendothelial collagen exposure followed by activation of tissue factors which ultimately induce arterial thrombosis. Interference with platelet aggregation has also been described to play a role. A third mechanism associated with sorafenib-induced ischemia has been proposed, with RAF inhibition activating two pro-apoptotic kinases involved in oxidant stress-induced injury in cardiomyocytes, making them more prone to ischemic damage [67].

The incidence of angina and myocardial infarction with bevacizumab, a monoclonal antibody against VEGF, varies in the literature from 0.6 to 1.5% [68, 69].

This toxicity has not been shown to be dose-dependent, and the median time to a coronary event is 3 months. Proposed risk factors include age >65 years and previous history of arterial thrombotic event [68].

Regarding antiangiogenic multi-targeted kinase inhibitors, in an observational study of 86 patients with metastatic renal cell carcinoma treated with sunitinib or sorafenib, 33.8% experienced a cardiovascular event, most of which were related to myocardial damage of varying degrees. Approximately half of the cases (16.2% of the total population) were asymptomatic and had cardiac enzyme elevations or electrocardiogram (ECG) changes. The remaining cases (17.6% of the total population) experienced mild to life-threatening clinical symptoms. Seven patients (9.4%) required intermediate or intensive care admission. As is discussed later, a high proportion of the patients in this study had at least one coronary artery disease risk factor [70].

Based on the data from phase III trials, 1–5% of patients treated with newer antiangiogenic multi-kinase inhibitors, such as axitinib, pazopanib, nintedanib, regorafenib, cabozantinib, and lenvatinib, have experienced acute coronary events [71–76].

Ponatinib is the multi-kinase inhibitor more associated to arterial thromboembolic events; hence, its FDA label includes a black box warning regarding this potential side effect. Coronary artery occlusion has been described in 21% of patients [77]. Patients treated with ponatinib have also experienced peripheral arterial occlusion (12%) and cerebrovascular arterial events (9%). These arterial events can be life-threatening and multisite. Arterial events can appear within the first 2 weeks of treatment; hence, close monitoring is advised. Arterial occlusion adverse events were more frequent with increasing age and in patients with history of ischemia or with vascular risk factors such as hypertension, diabetes, or hyperlipidemia. However, arterial vascular adverse events have been also described in 19% of young patients without vascular risk factors treated with ponatinib [77].

14.4 Cardiac Arrhythmias

Cancer patients are prone to arrhythmic events, secondary to systemic treatment as well as to other conditions and concomitant medications [78–80]. Fortunately, most arrhythmogenic events are not clinically significant rhythm alterations; however, in some cases, life-threatening arrhythmias can occur. Their early identification and treatment as well as correction of the associated risk factors are essential [79, 80].

14.4.1 QT Interval and Prolonged QTc Interval-Associated Arrhythmias

14.4.1.1 QTc Interval Prolongation: Definition and Physiopathology

The QT interval is measured from the beginning of the QRS complex to the end of the T wave [81, 82] (Fig. 14.1) and represents ventricular activation and recovery

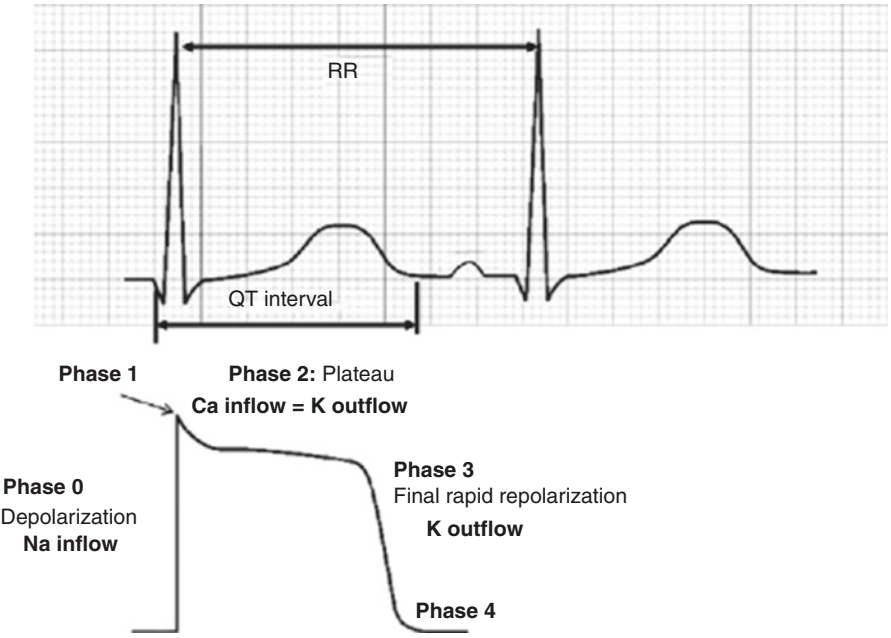

Fig. 14.1 QT interval and its correlation with ventricular action potential. QT interval is measured from the beginning of the QRS complex to the end of the T wave; RR is the interval from the onset of one QRS complex to the onset of the next QRS complex. The lower part of the figure shows the correlation between QT interval and ventricular action potential: phase 0 or depolarization is mainly caused by sodium influx into the cells, while in phase 2 or plateau, there is equilibrium between calcium influx and potassium efflux. Phase 3 or rapid final repolarization is caused by a potassium efflux

(depolarization and repolarization) on an ECG. Depolarization is a result of sodium and calcium influx into the cardiomyocyte. Conversely, when potassium efflux exceeds sodium and calcium influx, repolarization occurs [81]. Any drug affecting these channels, especially hERG potassium channels involved in potassium efflux during repolarization [83], can potentially cause changes in the QT interval [84, 85]. Additionally, electrolytic disturbances may also interfere in the normal process of depolarization and repolarization [78, 79].

The QT interval is prolonged with slower heart rates and shortened with faster rates. To avoid the variability associated with heart rate, several formulas have been developed which mathematically correct the QT interval, known as the "QTc interval" [10, 78, 79, 81, 86] (Table 14.3). This is the most common measurement used to evaluate the arrhythmogenic potential of a drug secondary to repolarization interference. There is currently no agreement regarding which is the most appropriate method. Automatic measurements usually provide QTc intervals adjusted according to the Bazett formula. This formula is known to overestimate QTc interval at high heart rates, while the Fridericia formula seems to be more accurate in this setting [87, 88].

Table 14.3 QTc interval correction formulas

Reference	Formula
Fridericia [92, 196]	$QT_F = QT/RR^{1/3}$
Bazett [92, 197, 198]	$QTc = QT/RR^{½}$
Framingham (Sagie) [199]	$QT_{LC} = QT + 0.154\ (1–RR)$

RR interval from the onset of one QRS complex to the onset of the next QRS complex

Table 14.4 Drugs inducing QTc interval prolongation

Drug class	Known drugs
Serotonin agonists/ antagonists	Cisapride, ketanserin, zimeldine
Antibiotics	Clarithromycin, erythromycin, gatifloxacin, sparfloxacin, pentamidine
Antifungal	Ketoconazole, miconazole, itraconazole
Antipsychotics	Phenothiazine, droperidol, haloperidol, pimozide, ziprasidone, olanzapine, risperidone
Antidepressants	Amitriptyline, clomipramine, desipramine, imipramine, sertraline, venlafaxine
Vasodilators	Bepridil, perhexiline
Antiarrhythmic drugs	IA: Procainamide, quinidine, amaline, disopyramide
	IC: Flecainide, propafenone
	III: Amiodarone, sotalol, dofetilide, ibutilide
Other	Methadone

An international consensus regarding what can be considered as normal versus prolonged QTc intervals is also currently lacking. Generally, QTc intervals ≤430 for males and ≤450 milliseconds (ms) are considered normal, while QTc intervals >450 ms in men and >470 ms in woman are considered prolonged [78, 79]. These different values reflect the physiological variation of the QTc interval between genders [89]. Based on experience in patients with congenital long QT syndrome, it is considered that the risk of ventricular arrhythmias, particularly torsade de pointes, is increased when the QTc interval exceeds 500 ms [88]; however, there is no threshold below which the QTc interval prolongation is considered free of pro-arrhythmic risk [78].

While several anticancer agents which induce QTc interval prolongation have been identified, a review of the literature shows other conditions with the potential to cause prolongation are commonly associated with cancer patients. This includes concomitant medications (Table 14.4), other comorbidities, and electrolytic disturbances [79, 86, 88, 90] (Table 14.5). Identification and correction of any reversible risk factors present in a patient is paramount to limiting additional toxicity when prescribing drugs with the potential to prolong the QTc interval.

Table 14.5 Drug-induced QTc interval prolongation risk factors

Parameter	Risk factor
Gender	Female
Related to drug administration	High drug concentration
	Rapid rate of intravenous infusion with a QT-prolonging drug
Electrolyte disturbances	Hypocalcemia
	Hypokalemia
	Hypomagnesemia
Previous cardiovascular disease	Myocardial ischemia
	Cardiac hypertrophy
	Congestive heart failure
	Bradycardia
	Atrioventricular block
	Myocarditis
Baseline ECG alteration	Subclinical long QT syndrome
	Baseline QT prolongation
Endocrine disorders	Hyperaldosteronism
	Hypothyroidism
	Hyperparathyroidism
Neurologic disorders	Stroke
	Subarachnoid hemorrhage
	Intracranial trauma
Other diseases	Diabetes
	Cirrhosis

After the post-marketing withdrawal of several chemically unrelated drugs in the early 1990s due to their arrhythmogenic risk secondary to QTc interval prolongation [91], evaluation of drug-induced QTc interval changes became a clinical issue for both anticancer agents and other medications. The *International Conference Harmonization Guideline for the clinical evaluation of QT interval prolongation and pro-arrhythmic potential for non-anti-arrhythmic drugs* (ICH E14) was published in 2005 [92]. This guideline requires every new drug to undergo clinical assessment for its repolarization effects before entering phase II trials. Nonetheless, such guidelines have limitations when evaluating anticancer agents, as in most cases, studies cannot be performed in healthy volunteers, and thus, studies including placebo are likely to be unethical [78, 88, 93].

Furthermore, the risk-benefit balance must be taken into account when evaluating anticancer drugs. Thus, while drugs such as terfenadine were removed from the market for inducing a mean QTc interval prolongation of 6 ms, approval has been maintained for others with similar or longer intervals. Examples include the antiemetic granisetron which induces a 5 ms mean QTc interval prolongation [88], and drugs, such as nilotinib or romidepsin, approved on the basis of their efficacy despite inducing mean QTc interval prolongations of 10 ms [94] and 14 ms [95], respectively.

14.4.1.2 Anticancer Agents Associated with QTc Interval Prolongation

Both classic chemotherapeutic agents and targeted therapies have been shown to induce QTc interval prolongation [96]. The agents more associated to QTc interval prolongation and their main effects are listed in Table 14.6.

Table 14.6 Anticancer agent-induced QTc interval prolongation

Drug	Effect measured[a]	Percentage of patients/interval duration	Reference
Chemotherapeutic agents			
Arsenic trioxide	QTc interval prolongation (any grade)	38.4%	Barbey et al. [102]
	QTc interval prolongation ≥500 ms	26.5%	Barbey et al. [102]
	Ventricular tachycardia	4 of 14 patients	Ohnishi et al. [200]
Anthracyclines	QTc prolongation after first dose	11.5%	Pudil et al. [99]
	QTc prolongation 6 months after chemo	34.6%	Pudil et al. [99]
Histone deacetylase inhibitors			
Romidepsin	Mean QTc prolongation	14 ms	Piekarz et al. [95]
	QTc prolongation 480 ms (grade 2)	10%	Bates et al. [88]
Vorinostat	QTc prolongation grade 2	1–3%	Munster et al. [109]
	QTc prolongation grade 3	0.8–4%	
	QTc prolongation >60 ms from baseline	2%	
Panobinostat			
IV, daily × 7 days every 3 weeks	DLT due to QTc interval prolongation >500 ms	4 of 6 patients	Giles et al. [112]
	Grade 2 QTc interval prolongation	1 of 2 patients	
IV, day 1, 3, and 5 every 3 weeks. Dose 20 mg	QTc interval prolongation >500 ms	1 of 44 patients	Zhang et al. [111], Sharma et al. [113]
	QTc interval prolongation 480–500 ms	2 of 44 patients	
LAQ824	Mean QTc prolongation	14 ms	De Bono et al. [201]
Plitidepsin	Mean QT prolongation	2.51 ms	Soto-Matos et al. [175]
Kinase inhibitors			
Multi-targeted antiangiogenic tyrosine kinase inhibitors			
Vandetanib			
Single agent			Tamura et al. [202]
Single-agent dose 100 mg	QTc interval prolongation (any grade)	23%	

(continued)

Table 14.6 (continued)

Single-agent dose 200 mg	QTc interval prolongation (any grade)	50%	
	Grade 3	5%	
Single-agent dose 300 mg	QTc interval prolongation (any grade)	47%	
	Grade 3	5%	
Combination with docetaxel NSCLC			Heymach et al. [203]
Control arm (docetaxel)	Median QTc interval prolongation after 6 weeks of treatment	2 ms	
Vandetanib 100 mg + docetaxel	Median QTc interval prolongation after 6 weeks of treatment	14 ms	
	QTc interval prolongation grade 3 or more	5%	
Vandetanib 300 mg + docetaxel	Median QTc interval prolongation after 6 weeks of treatment	26 ms	
	QTc interval prolongation grade 3 or more	11%	
Sunitinib	Torsade de pointes	<0.1%	Food and Drug Administration [116]
	QTc interval > 500 ms QTc interval prolongation >60 ms from baseline	0.5% 1%	Shah et al. [53]
Cabozantinib	Mean QTc interval prolongation	10–15 ms	Shah et al. [117]
Pazopanib	Conflicting data		Shah et al. [53]
	Phase III studies QTc interval prolongation (pazopanib group) [QTc interval prolongation placebo 13%] QTcB >500 ms Torsade de pointes two cases (one of them on amiodarone)	18% 2.0% 0.2%	
	Dedicated QTc interval study Mean QTc prolongation QTc interval prolongation >60 ms from baseline QTc interval > 500 ms	4.4 ms 0 0	

Table 14.6 (continued)

Sorafenib	Mean QTc prolongation	8.5 ms	Shah et al. [53]
	Mean QTc prolongation (statistically significant)	10 ms	Kloth et al. [118]
Multi-targeted tyrosine kinase inhibitors—targeting Bcr-Abl			
Nilotinib	QTc interval prolongation >30 ms from baseline	33–40.8%	Hazarika et al. [204]
	QTc interval prolongation >60 ms from baseline	1.9–2.5%	
	QTc interval prolongation >60 ms from baseline QTc interval >500 ms	3.9% 0.9%	Shah et al. [53]
Dasatinib	Mean QTc interval changes	7.0–13.4 ms	Food and Drug Administration [119]
	QTc interval prolongation <30 ms from baseline	54%	Johnson et al. [205]
	QTc interval prolongation 30–60 ms from baseline	36%	
	QTc interval prolongation >60 ms from baseline	11%	
	QTc interval prolongation 450–500 ms	21%	
	QTc interval prolongation >500 ms	1%	
Imatinib	Mean QTc prolongation (statistically significant)	10 ms	Kloth et al. [118]
Bosutinib	QTc interval prolongation (any)	37%	Abbas et al. [120]
	QTc interval >500 ms Mean QTc interval prolongation	0.2% 3 ms	Kloth et al. [118]
ALK inhibitors			
Ceritinib	QTc interval prolongation >60 ms from baseline	5.3%	Shah el at. [117]
Crizotinib	QTc interval prolongation >500 ms QTc interval prolongation >60 ms from baseline	1.5% 3%	Shah et al. [53]
TSR-011	QTc interval prolongation • 40 mg Q 8 h (recommended phase II dose) QTc interval prolongation >500 ms 40 mg Q 8 h (recommended phase II dose)	15.9% 7.7% 4.3% 0%	Arkenau et al. [121]

(continued)

Table 14.6 (continued)

BRAF inhibitors			
Vemurafenib	Any QTc interval prolongation QTc interval prolongation >500 ms	10% 1.6–2%	Shah et al. [53]
	Clinically relevant QTc interval prolongation	34.4%	Kloth et al. [118]
Tyrosine kinase inhibitors targeting EGFR—HER2			
Lapatinib	QTc interval prolongation >500 ms QTc interval prolongation >60 ms from baseline	6% 11%	Shah et al. [53]
Rociletinib	QTc interval prolongation (any) • 500 mg BID • 625 mg BID QTc interval >500 ms from baseline • 500 mg BID • 625 mg BID	21% 28% 5% 9.5%	Goldman et al. [123]
Osimertinib	QTc interval prolongation >500 ms QTc interval prolongation >60 ms from baseline	0.2% 2.7%	Food and Drug Administration [122]
Erlotinib	QTc interval prolongation (statistically significant)	9 ms	Kloth et al. [118]
	No evidence of effect on QTc interval		Shah et al. [53]
Checkpoint kinase 1 inhibitor			
MK-8776	QTc interval prolongation QTc interval >500 ms from baseline	19% 2%	Daud et al. [129]
Insulin growth factor receptor			
Linsitinib (OSI-906)	QTc interval prolongation	20%	Quinn et al. [130]
Protein kinase C inhibitors			
Enzastaurin			
Single agent			
800 mg daily	QTc interval prolongation grade 3	1 out of 9	Kreisl et al. [133]
250 mg twice daily	QTc interval prolongation grade 3	1 out of 5	
Multiple doses	QTc interval prolongation grade 1–2	23%	
350 mg twice daily	QTc interval prolongation grade 2	1 out of 7	Rademaker-Lakhai et al. [131]

Table 14.6 (continued)

500–525 mg daily	QTc interval prolongation grade 2		Kreisl et al. [134]
500 mg daily	QTc interval prolongation >50 ms from baseline	5%	Oh et al. [135]
Multiple doses (healthy volunteers)	QTc interval prolongation >450 ms	1 out of 25	Welch et al. [132]
	QTc interval prolongation >30 ms from baseline	5 out of 25	
Combination with capecitabine			
Enzastaurin 350 mg	QTc interval >500 ms	1 out of 7	Camidge et al. [206]
Multiple doses	QTc interval prolongation grade 1–2	23%	
HSP90 inhibitors			
HSP990	QTc interval >500 ms	3%	Spreafico et al. [124]
AUY922	QTc interval > 450 ms QTc interval > 480 ms	23% 2%	Sessa et al. [125]
PF-04929113	QTc interval prolongation (any) QTc interval > 450 ms	16% 2%	Reddy et al. [127]
Other agents			
Lonafarnib	QTc interval prolongation grade 3	1 out 15 patients	Hanrahan et al. [136]
Combretastatin A4 Phosphate	QTc interval prolongation grade 1–2	5%	Dowlati et al. [137]
Bortezomib			
Goserelin-bicalutamide	QTc interval prolongation 30–60 ms from baseline	46%	Garnick et al. [140]
	QTc interval prolongation >60 ms from baseline	8%	
Leuprolide-bicalutamide	QTc interval prolongation 30–60 ms from baseline	26%	Garnick et al. [140]
	QTc interval prolongation >60 ms from baseline	6%	

DLT dose-limiting toxicity
[a]Graded according to NCI-CTCAE, version 3

Chemotherapeutic Agents

Anthracyclines have been associated with prolonged QTc intervals and an increased arrhythmogenic risk [97–99]. Even years after having received chemotherapy, women receiving anthracycline-pretreatment for breast cancer have been observed to have longer baseline QTc and significant differences in QTc interval prolongation after isoflurane anesthesia [100].

The chemotherapeutic agent most closely associated with QTc interval prolongation is probably arsenic trioxide. Its potential to induce QTc interval prolongation was first described in an acute promyelocytic leukemia study in which 16 of the 40 enrolled patients experienced QTc interval prolongation >500 ms, accompanied in

one case by a single, asymptomatic, brief, self-limited episode of torsade de pointes [101]. Pooled analysis of 99 patients enrolled in phase I and II trials with arsenic trioxide showed that 38 patients experienced QT interval prolongation, 26 of whom experienced QT interval prolongation >500 ms. Arsenic trioxide-induced QTc interval prolongation is reversible before the following cycle, is dose-dependent, and is also more likely to occur in females, in patients with hypokalemia, or those with an underlying heart disease [102].

Other chemotherapeutic agents associated with QTc interval prolongation are amsacrine [96], 5-fluouracil, generally in the context of a coronary event [103, 104], and cyclophosphamide [105]. The magnitude of QTc interval prolongation associated with cyclophosphamide appears to correlate with further risk of heart failure.

Histone Deacetylase Inhibitors

Histone deacetylase (HDAC) inhibitors are a group of compounds which modulate histone acetylation which ultimately induces epigenetic changes in transcription. Several chemically unrelated HDAC inhibitors induce QTc interval prolongation. The first HDAC inhibitor which showed arrhythmogenic potential was romidepsin, also known as depsipeptide. A phase II study of romidepsin in metastatic neuroendocrine tumors was prematurely terminated as two patients experienced ventricular tachycardia, and a sudden death was described in a third patient [106]. Pooled analysis of NCI-sponsored clinical trials, including more than 500 patients, showed a 10% incidence of QTc interval >480 ms [88]. Moreover, the mean QTc interval prolongation in the cardiac sub-study of a phase II trial of romidepsin in T-cell lymphoma was 14 ms [95]. Romidepsin, now approved for T-cell lymphoma, merits further development which takes into account QTc data; Food and Drug Administration (FDA) approval includes several recommendations regarding QTc interval monitoring and management of its potential prolongation [107].

Vorinostat, a phenylbutyrate-derived HDAC, led to a QTc interval >470 ms in one of 74 patients enrolled in a phase II study in refractory T-cell lymphoma [108]. The incidence of grade 2 QTc interval prolongation according to CTCAE v3.0 was 1–3% and that of grade 3 was 0.8–4% [109]. A dedicated phase I cardiac study in advanced solid tumors showed that a single overdose of vorinostat did not significantly increase QTc interval [109]. FDA approval includes a specific recommendation for electrolyte monitoring prior to vorinostat administration to diminish the risk of QTc interval prolongation and arrhythmia [110].

Another chemically unrelated molecule, panobinostat, showed dose- and schedule-related QTc interval prolongation, with a much higher incidence of grade 3 QTc interval prolongation observed following daily intravenous administration compared to the intermittent schedule [111–113].

Kinase Inhibitors

QTc interval prolongation was first described with multi-targeted kinase inhibitors such as vandetanib or sunitinib. In recent years, the spectrum of kinase inhibitors

inducing QTc interval prolongation has widened, including both multi-targeted and specific kinase inhibitors.

Antiangiogenic Multi-targeted Kinase Inhibitors

Several approved multi-targeted kinase inhibitors have the potential to induce QTc interval prolongation [79]; all of them have shown in vitro to interact with HERG K^+ channels. In the phase III randomized trial evaluating vandetanib in medullary thyroid cancer [114], vandetanib induced any QTc interval prolongation in approximately 14% of patients, but only 8% had grade 3 QTc interval prolongations, which are at higher risk of developing a ventricular arrhythmia [115]. Hence, vandetanib FDA approval incorporates specific guidelines for QTc interval, electrolyte monitoring, and dose adjustment in the event of QTc interval prolongation [115].

Other antiangiogenic multi-targeted kinase inhibitors, such as sunitinib, sorafenib, or cabozantinib, have shown a potential to prolong QTc interval but to a lesser extent [53]. In addition to induce a clinically relevant QTc interval prolongation (>500 ms in 0.5% of patients), sunitinib has been associated to inducing torsade de pointes in <0.1% of patients [116]. Hence, the FDA label recommends the use of sunitinib with caution in patients with electrolyte disturbances, previous history of QT interval prolongation, or other pre-existing cardiac conditions. Cabozantinib and sorafenib have shown to modestly increase mean QTc interval [53, 117, 118] (Table 14.6). The effect of pazopanib on the QTc interval is unclear. A dedicated study to evaluate the effect of pazopanib on QTc interval did not show any significant effect [53]. However, 18% of the patients treated with pazopanib in phase III trials experience QTc interval prolongation to some extent; while, 13% of patients in the placebo group experienced QTc interval prolongation. According to Shah et al., 2 of 977 patients treated with pazopanib experienced torsade de pointes, and one of them was taking an antiarrhythmic drug that might have had a causal effect in the event [53].

Abr-Bcl and Src Multi-kinase Inhibitors

Nilotinib and dasatinib, both ABL1 inhibitors, have been associated with heart failure and QTc prolongation (Table 14.6), with specific guidelines for the toxicity monitoring and management in their FDA label, respectively [94, 119].

Regarding bosutinib, while a dedicated study did not show any effect on QTc [117], a phase I study to evaluate bosutinib safety in patients with liver dysfunction revealed QTc interval prolongation in 10 of the 27 participating patients. Although the incidence of QTc interval prolongation in this study increased with declining liver function, one of nine healthy volunteers experienced QTc prolongation (453 ms, 16 ms increase from baseline). In none of the patients, QTc interval reached 500 ms [120].

ALK Inhibitors

Several anaplastic lymphoma kinase (ALK) inhibitors have shown a potential to increase QTc interval. According to the FDA label, crizotinib increases QTc interval above 500 in 1.5% of patients [53]; while ceritinib induces QTc interval

prolongation >60 ms from baseline in 5.3% of patients [117]. Other novel compounds, such as TSR-011, induced QTc prolongation in a dose-dependent manner [121].

BRAF Inhibitors

A recent retrospective multicentric study evaluated the changes induced by different kinase inhibitors—namely, erlotinib, gefitinib, imatinib, lapatinib, pazopanib, sorafenib, sunitinib, and vemurafenib—on QTc interval [118]. Patients treated with vemurafenib had the most clinically significant QTc interval prolongation, as 34.3% of them experienced QTc interval prolongation >30 ms from baseline and 11.9% of patients treated with vemurafenib had a QTc > 470 ms.

Tyrosine Kinase Inhibitors Targeting EGFR and HER2

The retrospective multicentric study, evaluating the effect of different kinase inhibitors on QTc interval, revealed a statistically significant increase in mean QTc interval in the 21 patients treated with erlotinib [118]. However, only three patient had a QTc interval increase >30 ms, and two had a QTc that achieved 470 ms which were the predefined criteria for clinically relevant QTc interval increase.

In the same retrospective study, lapatinib did not show to induce any significant increase in QTc interval [118]. However, the number of lapatinib-treated patients in the analysis was limited. In the phase I study of lapatinib, 11% of the 81 treated patients experienced a QTc interval prolongation >60 ms from baseline, and 6% of patients had an on-treatment QTc interval >500 ms. Hence, the FDA label recommends caution when administering lapatinib to patients with concomitant risk factors to develop QTc interval prolongation [53].

Osimertinib and rociletinib, both novel EGFR inhibitors targeting T790 M resistance mutation, have shown to induce a concentration/dose-dependent QTc interval prolongation. In clinical trials, osimertinib and rociletinib induced QTc interval greater than 500 ms in 0.2% and 5% patients, respectively [122, 123]; hence, ECG monitoring is recommended in patients treated with this agents with concomitant risk factors to develop QTc interval prolongation.

HSP90 Inhibitors

Different HSP90 inhibitors have shown QTc interval prolongation as an adverse event which limited dose escalation. In the phase I of HSP990, 3% of patients had QTc interval greater than 500 ms [124]; while, in the phase I of AUY922, 2% of patients had QTc interval greater than 480 ms [125]. The HSP90 inhibitor PF-04929113 did not show to induce any relevant QTc interval prolongation in the phase I in solid tumors [126]. However, in the phase I study in hematological malignancies, 16% of patients had some QTc interval prolongation, and 2% of patients had an on-treatment QTc interval >450 ms [127].

HSP90 inhibitors commonly induce diarrhea and electrolyte disturbance that might collaborate in QTc interval prolongation. However, HSP90 inhibitors might have a direct effect on QTc interval, as HSP90 is involved in ERG channels trafficking [128].

Other Agents

There is an increasing list of agents that can potentially prolong QTc interval which includes some checkpoint kinase inhibitors [129], IGF1 inhibitors [130], protein kinase C inhibitors (enzastaurin) [131–135], vascular disruptors (lonafarnib [136] and combretastatin A4 phosphate [137]), or Hdm-2 inhibitors (serdemetan) [138]. Regarding hormonotherapy, some agents also have the potential to prolong QTc interval [139, 140] (Table 14.6).

14.4.2 Other Chemotherapy-Induced Arrhythmias

Anticancer agents can induce arrhythmias not associated with QTc interval. Post-chemotherapy arrhythmias are actually one of the most common reasons for cardiology consultations in cancer centers [141]. A variety of arrhythmias have been reported, mainly sinus bradycardia, atrioventricular block, atrial fibrillation, and ventricular tachycardia; however, other less frequent arrhythmias have been described [80, 141].

Paclitaxel is the chemotherapeutic agent most commonly associated with rhythm disturbances, and the most frequent events are asymptomatic sinus bradycardia (29%) and first-degree atrioventricular block (25%) [142]. More severe conduction abnormalities are rare [143]; among 3400 patients in an NCI database, only four experienced second- or third-degree heart block [142]. Two potential mechanisms have been proposed: direct paclitaxel toxicity on the Purkinje system and secondary to histamine release induced by the Cremophor EL vehicle [142]. Although paclitaxel-induced arrhythmias were initially believed to be related to Cremophor, the vehicle used to increase paclitaxel water solubility, paclitaxel has pro-arrhythmogenic potential. Nab-paclitaxel, which does not require Cremophor, induces bradycardia in a small portion of patients (<1%) [144]. Other anticancer agents have been associated with rhythm disturbances, including 5-fluoraracil, cisplatin, gemcitabine, IL-2, anthracyclines, and melphalan [11] (Table 14.7).

14.4.2.1 Targeted Agent-Induced Rhythm Disturbances

Some targeted agents have been also associated to rhythm disturbances different to QTc interval prolongation, such as crizotinib and ponatinib. Crizotinib induces sinus bradycardia in 69% of the patients in a large retrospective cohort [145], while ponatinib induces arrhythmias in 19% of patients, according to the FDA label. Atrial fibrillation is the most common arrhythmia induced by ponatinib, described in 7% of patients treated with ponatinib [77].

14.5 Hypertension

Hypertension is one of the most common toxicities associated with VEGF pathway inhibitors for both monoclonal antibodies, such as bevacizumab, and multi-targeted tyrosine kinase inhibitors, such as sunitinib, sorafenib, axitinib, cediranib,

Table 14.7 Patients with chemotherapy-induced arrhythmia

Drug	Bradycardia	Atrial fibrillation	Ventricular tachycardia	Reference
Paclitaxel	29% bradycardia 25% first-degree atrioventricular block <0.1% second–third-degree atrioventricular block	0.18%	0.26%	Guglin et al. [141], Rowinsky and Donehower [142]
Fluorouracil	2.8%	4.2–6.5%	1.1%	De Forni et al. [61], Guglin et al. [141], Talapatra et al. [207]
Cisplatin	Case reports	Case reports	xx	Canobbio et al. [141], Altundag et al. [208], Canobbio et al. [209], Hashimi et al. [210]
Gemcitabine	2.3%	8.1%	1.6%	Gridelli et al. [211], Santini et al. [212], Sauer-Heilborn et al. [213], Zwitter et al. [214], Lin et al. [215]
Anthracyclines	3.4%	2.2–10%	6%	Steinberg et al. [11], Guglin et al. [141], Kilickap et al. [216, 217]
IL-2	1.08% Associated to poly-chemotherapy	4.3–13.3%	0.2–1.1%	Guglin et al. [141], Margolin et al. [218], Lee et al. [219]
Melphalan	5% In combination with bortezomib	6.6–11.8%	0.7–1.5%	Moreau et al. [220], Phillips et al. [221], Mileshkin et al. [222], Lonial et al. [223], Palumbo et al. [224]

aflibercept, and telatinib. Several mechanisms of action have been identified including VEGF pathway inhibition and endothelial cell apoptosis. Inhibition of the VEGF pathway decreases nitric oxide levels leading to vasoconstriction. This mechanism might be responsible for the rapid increase in blood pressure after anti-VEGF therapy initiation [146]. Additionally, sustained VEGF pathway inhibition induces endothelial cell apoptosis, which ultimately causes a reduction in the number of capillaries and increases overall vascular resistance. This second mechanism has been observed in patients treated with bevacizumab [147], sunitinib [148], and telatinib [149] and appears to be reversible within 2 weeks of treatment discontinuation [150, 151].

Incidence of drug-induced hypertension ranges from 15 to 25% with sunitinib [152, 153], 20% with sorafenib [154], and up to 35% with bevacizumab. The three agents induced dose-dependent hypertension [155, 156]. Hypertension can be associated to serious complications such as intracranial hemorrhage and hypertensive

urgency. Prior uncontrolled hypertension is a relevant risk factor for developing such complications; hence, blood pressure normalization prior to antiangiogenic treatment initiation is essential.

14.6 Venous Thromboembolic Disease

14.6.1 Chemotherapy and Targeted Agents

A number of agents are associated with an increased incidence of venous thromboembolic events, including cisplatin [157], vorinostat [108, 158], thalidomide [159, 160], and erlotinib [161]. In addition, antiangiogenic drugs have been associated to a venous thrombosis event incidence ranging 3–6% [53, 71, 74, 116]. Nonetheless, two meta-analysis comparing the incidence of venous thromboembolic events of patients treated in randomized phase II and III clinical trials with VEGFR-TKIs (sunitinib, sorafenib, pazopanib, and axitinib) did not showed a statistically significant difference between the patients treated in the VEGFR-TKIs arms and the control arms [162, 163]. It should be noted that patients treated with novel TKIs, such as cabozantinib and ponatinib, in which venous thromboembolic events have been described in up to 6% of the treated patients, were not included in none of the two meta-analyses [75, 77].

Proposed mechanisms for anticancer-induced venous thromboembolic events include alterations in platelet aggregation as well as direct effects on the endothelium [5]. The role of prophylactic administration of aspirin or low-molecular-weight heparin in this setting is uncertain, but antiaggregation or anticoagulation might benefit some high-risk patients [164].

14.6.2 Hormonotherapy

Tamoxifen, a selective estrogen receptor modulator (SERM), has been associated an increased incidence of thromboembolic events [165] and should be used cautiously in women with history of previous thromboembolic events. This higher risk has not been observed in the same patient population when treated with aromatase inhibitors. However, aromatase inhibitors are associated to a higher incidence of adverse cardiac events [166]. Some data suggest a cardioprotective role for tamoxifen, supporting these differences. Moreover, fulvestrant, an endocrine agent which degrades the estrogen receptor, also increases the risk of thromboembolic events [167].

14.7 Radiation-Induced Heart Disease

While it is not a systemic therapy, radiation therapy is included in the current review as it has been shown to increase toxicities secondary to systemic therapy. External radiation therapy to the mediastinum can induce toxicity in the pericardium as acute

pericarditis or asymptomatic chronic pericardial effusion within 12 months after radiotherapy, coronary arteries by inducing premature atherosclerosis in the coronary circulation, heart valves, and myocardium damage [168–170]. The underlying mechanism is microvascular destruction and apoptosis due to direct cellular injury which produces fibrosis in the years subsequent to therapy.

A number of factors have been associated with increased risk of cardiotoxicity such as radiation dose [4], heart volume exposed to radiotherapy, radiation delivery technique, and patient's age. Two large studies of survivors of childhood cancer show an increased risk of cardiotoxicity after radiation therapy with hazard ratios between 2 and 25 depending on the radiation doses [4, 171]. Incidence of cardiac damage from radiation has been reducing with improvements in radiation techniques. Novel radiotherapy delivery and positioning techniques, such as intensity-modulated radiation therapy, deep inspiration breath-hold technique, and prone positioning, might decrease the risk of direct cardiac damage. Regarding patients' age at the time of radiation, incidence of radiation-induced cardiotoxicity is higher in younger patients, as patients under the age of 20 years are apparently more susceptible to DNA damage [169, 172].

14.8 Cardiotoxicity Prevention and Management

As described in Fig. 14.2, several approaches are available to limit the occurrence of cardiotoxicity and to treat it optimally in the event that it does occur [6, 10, 173, 174].

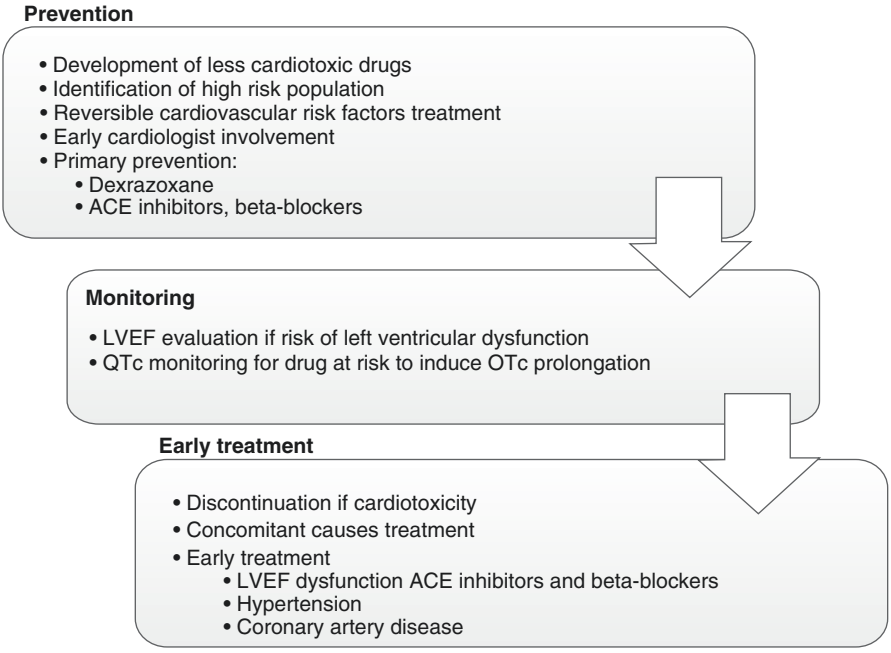

Fig. 14.2 Proposed algorithm for cardiotoxicity prevention, monitoring, and management

14.8.1 Prevention

14.8.1.1 Drug Development

Prevention of cardiotoxicity has been integrated into the early phases of drug development. Extensive efforts have been invested in the design of less cardiotoxic drugs. One of the pioneering approaches was the design of alternative anthracycline formulations such as epirubicin and liposomal anthracyclines; epirubicin is a semisynthetic epimer of doxorubicin with an improved cardiotoxic profile, while liposomal anthracycline formulations diminish the distribution of the drug into the heart [30]. More recent examples are nab-paclitaxel, in which paclitaxel is associated with albumin in an attempt to improve its activity and reduce its toxicity [144], and plitidepsin, a romidepsin analog which has reduced QTc interval prolongation in early phases of clinical development [175]. Regarding tyrosine kinase inhibitors, some of the cardiotoxic effects are thought to be a result of off-target effects of the drug, resulting from the inhibition of another kinase not involved in the drug's anticancer activity [176]. In some cases, drug reformulation to decrease its affinity for this off-target kinase could improve its cardiotoxic profile. The successfully redesigned formulation of imatinib for GIST is a good example of this approach [177].

Regulatory efforts have been also made to improve cardiac safety of new drugs. In addition to the guidelines described in this chapter for the evaluation of QTc interval during clinical development [92], specific guidelines have been issued for preclinical evaluation of the arrhythmogenic risk of non-antiarrhythmic drugs [178].

14.8.1.2 High-Risk Population Identification

Cardiovascular risk factors are often underestimated in cancer patients. Some studies revealed that a high proportion of patients have at least one cardiovascular risk factor; an observational study by Schmidinger et al. revealed that 48.8% of patients had hypertension, 26% had hypercholesterolemia, 22% had type 2 diabetes, and 12.8% had hypertriglyceridemia [70]. As has been described throughout this chapter, adequate control of these reversible risk factors and electrolyte disturbances is essential to diminish and control cardiotoxicity [79]. A recently published community-based retrospective cohort study showed that cardiovascular diseases are more frequent in long-term survivors of adult cancer onset than controls. Survivors from multiple myeloma, lung cancer, non-Hodgkin lymphoma, and breast cancer have a higher risk compared with non-cancer controls. This risk is even higher in patients with two or more cardiovascular risk factors [59]. Early involvement of cardiologists in the clinical management should be encouraged in patients with a pre-existing heart condition or those taking drugs that can induce left ventricular dysfunction or QTc interval prolongation [79].

14.8.1.3 Primary Prevention

Two randomized studies have evaluated antihypertensive medication as preventive treatment for chemotherapy-related cardiomyopathy, one using enalapril and the other using carvedilol. Cardinale et al. evaluated the effect of enalapril on patients experiencing troponin I elevation shortly after receiving chemotherapy. This study considered acute myocardial injury, measured as troponin elevation, as a potential

predictive marker of ventricular dysfunction [179]. Results showed a significantly reduction in the incidence of left ventricular dysfunction at 12 months with enalapril compared to placebo ($p < 0.001$). In a smaller study by Kalay et al., 25 patients treated with anthracyclines were randomly assigned to beta-blocker treatment (carvedilol) or placebo. Patients assigned to carvedilol experienced a lower incidence of anthracycline-induced myocardiopathy at 6 months. These studies suggest that optimizing hemodynamic and neurohumoral status before left ventricular dysfunction onset could be beneficial, and these two agents might be preferred treatment for hypertension in this setting [180].

Another primary prevention measure is the use of dexrazoxane, which is an iron chelator similar to ethylenediaminetetraacetic acid, although dexrazoxane has been shown to reduce heart failure incidence in children and adults treated with anthracyclines [181]. However, concerns have been raised about a possible increased risk of secondary malignancies and a potential decrease in antitumor efficacy. In light of these findings, the FDA has limited its use only in metastatic setting to cumulative doxorubicin doses exceeding 300 mg/m^2 [182].

14.8.2 Monitoring

14.8.2.1 Left Ventricular Ejection Fraction Evaluation

Cardiac assessment prior, during, and after systemic treatment is a matter of controversy. Several guidelines and algorithms have been published on this topic. Currently, LVEF is the most accepted parameter that predicts short-term and long-term mortality from cardiovascular events; however, LVEF remains relatively insensitive for detecting early stage cardiotoxicity. Two-dimensional (2D) biplane Simpson echocardiography is the method of choice for estimation of left ventricular volumes and ejection fraction during cancer treatments, based on its wide availability and lack of radiation. The main limitation of 2D echocardiography is its relatively moderate reproducibility.

Other useful echocardiographic technique is deformation imaging. Recent studies reported that a reduction of the global systolic longitudinal myocardial strain (GLS) accurately predict a decrease in LVEF during cancer treatment [183]. Although GLS may be a more sensitive tool to detect cardiotoxicity, currently there is no evidence to stop cancer treatment or to start with cardiac treatment based on a GLS decrease alone. Multiple-gated acquisition (MUGA) scans also are an option to monitor cardiac function; however, there are some limitations of this technique, mainly the exposition of the patient to radiation and providing limited information on diastolic function and cardiac structure [170]. Magnetic resonance imaging is considered the gold standard for the evaluation of systolic function, cardiac volumes, and mass, but it is not routinely used due to the high cost and lack of availability.

Doxorubicin is a good example of the use of LVEF monitoring. The FDA label for doxorubicin defines a 10% decline in LVEF below the lower limit of normal, a 20% decline in LVEF at any level, or a LVEF below 45% as an indicator for cardiac

function deterioration in adults and therefore anthracycline discontinuation. In children, anthracyclines should be discontinued in case of an absolute decrease in fractional shortening by ≥10% from baseline, or to <29%, or an absolute decrease in LVEF ≥10% from baseline or to <55%. Cardiac monitoring should include the patient's medical history, physical examination focusing on signs and symptoms of heart failure, and LVEF assessment by echocardiography or radionuclide angiography. For patients without increased risk of cardiotoxicity, an estimation of LVEF after the patient has completed four to five chemotherapy cycles (200–300 mg/m^2 of doxorubicin or equivalent) is recommended to identify patients with an asymptomatic decrease in systolic function and then reconsider further therapies. Patients at higher risk should be monitored more frequently [5].

There is no consensus in the diagnosis of cardiotoxicity. According to the European Society of Cardiology, a decrease in LVEF by >10% below the lower limit of normal (considered as a LVEF <50%) is diagnostic for cardiotoxicity, and ACE inhibitors and beta-blockers are recommended to prevent further LV dysfunction or symptomatic heart failure [184]. In addition, a less cardiotoxic regimen should be considered. Studies of optimal monitoring intervals to maximize sensitivity and specificity for detection of anthracycline-related cardiomyopathy are unclear, and further investigation will be extremely valuable.

14.8.2.2 Serum Cardiac Biomarkers

In addition to imaging techniques, a number of serum cardiac markers have evaluated in the last two decades. Serum troponin I levels are thought to reflect myocyte death and correlate with cumulative doxorubicin dose and congestive heart failure. For example, elevation of troponin I levels assessed before chemotherapy, during the 72 h after the end of chemotherapy (early evaluation), and 1 month after chemotherapy administration (late evaluation) predicted a late decline in LVEF and cardiac events and permitted to identify three different troponin release patterns. Similar results with troponin T have been documented [185, 186]. In patients treated with trastuzumab, troponin I elevation can also identified patients who are going to develop LVEF decline and who will not recover despite treatment with ACE inhibitors and beta-blockers [187]. In patients with breast cancer, a small single-center study demonstrated that the combination of high-sensitivity troponin with GLS provide a negative predictive value of 91% to predict cardiotoxicity [188]. Elevated B-type natriuretic peptide (BNP) levels after anthracycline administration may also correlate with left ventricular dysfunction and clinical heart failure. Due to interindividual variability, the role of BNP monitoring is still unclear. Larger prospective studies are required to evaluate the utility of these serum markers before incorporating them into general practice for patients receiving potentially cardiotoxic therapy [189–191].

14.8.2.3 QTc Interval Assessment

As previously noted, specific guidelines for drugs undergoing clinical development have been issued, ensuring evaluation of QTc interval changes related to drug administration. In addition, a number of approved drugs known to induce QTc

interval prolongation, such as romidepsin, vandetanib, or nilotinib, include specific recommendations for cardiac monitoring during administration in the FDA label [94, 107, 115].

14.8.3 Early Treatment

Any anticancer drug should be immediately discontinued in case of cardiovascular event, such as a significant decrease in LVEF or the occurrence of a QTc interval > 500 ms or QTc prolongation >60 ms from baseline. Exposure to other QT-prolonging drugs should be minimized and electrolyte abnormalities corrected. Unusually, bursts of torsade de pointes occur, requiring isoprenaline or transvenous pacing in order to obtain a heart rate > 90 beats per minute to prevent new episodes in the acute setting.

In case of LV dysfunction, there is little information available regarding cardiac dysfunction once treatment is established. An observational study showed an improvement in LVEF in patients with LVEF ≤45% if treatment with enalapril and carvedilol was established during the 6 months after completion of anthracycline treatment [192]. A number of studies have evaluated the effect of enalapril in childhood cancer survivors with asymptomatic cardiac dysfunction. Although temporary improvement of LVEF has been observed, it is unclear whether this would impact the global outcome in the future [193, 194].

No specific guidelines have been issued for chemotherapy-induced heart failure treatment, but it is widely believed that evidence-based guidelines for the general population would also be useful for cancer patients, despite not having been specifically validated in this setting. In individual cases with reasonable prognosis and good quality of life, an implanted cardioverter-defibrillator [195] and cardiac resynchronization therapy may be used to improve left ventricular dysfunction. Data regarding the potential use of stem cell therapy for anthracycline-induced cardiomyopathy treatment are yet to be published.

Conclusions

Cancer patients have an increased risk of developing heart disease as a result of chemotherapy, targeted therapies, and radiation therapy. Cardiovascular disease is currently the second leading cause of long-term morbidity and mortality among cancer survivors. Individuals at a high risk of developing such toxicity need to be identified prior to treatment initiation to minimize this risk through cardioprotective measures or modifications to the proposed treatment regimen. Cardiovascular monitoring is essential, both during and after antineoplastic treatment, for early detection and effective management of cardiotoxicity.

An interdisciplinary approach termed cardio-oncology or onco-cardiology is definitely needed. This discipline has been developed to ensure optimal patient outcomes by aligning oncologist and cardiologist efforts to optimize patients care while on active treatment and while on surveillance after treatment.

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Bone Marrow Toxicity: Red Blood Cells

15

Pere Gascon

Abstract

Anemia is a common manifestation in patients with cancer. Its cause can be multifactorial: the cancer itself, chemotherapy treatments, infiltration of bone marrow by cancer cells, hemolysis, nutritional deficiencies, blood loss, inflammation, and so forth. A major consequence of anemia is fatigue, a symptom that impacts the quality of life of cancer patients, and it can also compromise patients' compliance with their treatments. A new generation of anticancer agents, antitargeted therapies, is widely used in oncology. Some of these new agents are associated with anemia, although their mechanism is not yet understood.

We now have different options to correct chemotherapy- or cancer treatment-induced anemia: red blood cell (RBC) transfusions, iron, and erythropoiesis-stimulating agents (ESAs). Their safety profile is good if we know when and how to administer them.

Red blood cell transfusions are reserved for critical situations, when the patient presents with symptomatic severe anemia. In addition to the possibility that the RBCs carry viruses and other pathogens, some new alarm signals associated with their use have been raised over the last few years and are currently being investigated. Of particular concern are RBCs that have been stored for more than 2 weeks in the blood banks. Apparently, they lose some of their oxygen-carrying capacity and their ability to cross the capillaries.

Iron has long been an agent used to correct the anemia of blood loss. Recently, however, the administration of intravenous iron has become more popular, because the new preparations do not provoke the allergic and anaphylactic reactions seen with the old preparations. Intravenous iron is now being used in com-

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M. A. Dicato, E. Van Cutsem (eds.), *Side Effects of Medical Cancer Therapy*,
https://doi.org/10.1007/978-3-319-70253-7_15

bination with ESAs to produce faster and more robust corrections of anemia in the so-called functional iron deficiency, a type of anemia associated with chronic diseases and inflammation. In this condition there is a need for soluble iron, because one of the factors released during inflammation is hepcidin, a peptide that blocks the absorption of oral iron in the duodenum.

Finally, oncologists can utilize ESAs (recombinant human erythropoietin) for chemotherapy-induced anemia. Although they have been used for more than 20 years, over the last 8 years, several alarm signals have been associated with them. Their safety has been questioned after few clinical trial publications reported a poor outcome in patients receiving these agents in comparison to the control arm without ESAs. Many hypotheses have been suggested: ESAs would promote tumor growth via the presence of EPO receptors in cancer cells, a fact seriously questioned by recent publications; ESAs induce thromboembolic events; and so on. Another adverse event associated with the use of ESAs is pure red cell aplasia, in which the ESA molecule undergoes some structural changes due to physical or chemical conditions, causing the development of anti-EPO antibodies. This situation has been described only in patients with chronic renal failure receiving ESAs. The latest meta-analysis on ESAs regarding adverse events concludes that as long as ESAs are being used according to registry specifications in the setting of chemotherapy-induced anemia and the level of hemoglobin does not go beyond 12 g/dL, their use is safe.

Keywords

Anemia · Red blood cell transfusions · Iron · Erythropoiesis-stimulating agents Adverse events · Pure red cell aplasia · Erythropoietin · Thromboembolic events

15.1 Frequency and Causes of Anemia in Oncology

Anemia is a common manifestation in patients with cancer. More than 80% of cancer patients undergoing chemotherapy develop anemia (hemoglobin [Hb] level < 12 g/dL) [1]. Information on the prevalence and effects of anemia can be found in the literature from clinical trials of anemia treatments or chemotherapy [2–7]. The data generated by these studies came from well-designed and selected populations of patients. However, little was known about what happens day to day in doctors' offices or hospitals until the European Cancer Anaemia Survey (ECAS) study was published [1]. This study, in which 15,367 patients were evaluated, is probably the best ever performed to understand the incidence and prevalence of anemia in cancer patients. This prospective study demonstrated a prevalence of anemia at enrollment of 39.3% (Hb < 10.0 g/dL, 10%) and 67.0% during the survey (Hb < 10.0 g/dL, 39.3%). Low Hb levels were found to correlate with poor performance status. Incidence of anemia was 53.7% (Hb < 19 g/dL, 15.2%).

Anemia in the cancer patient can be caused by a variety of conditions in what constitutes the so-called anemic syndrome, either caused by the same tumor or by

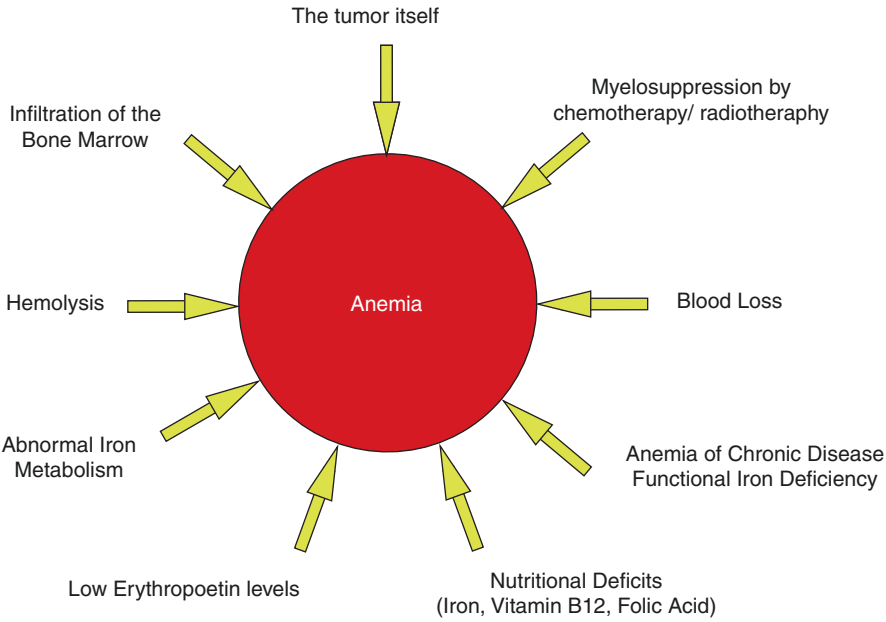

Fig. 15.1 Causes of anemia in the patient with cancer (adapted from [2, 8, 9])

the effects or complications of cancer treatments [1]. The causes of anemia are multifactorial: (1) bone marrow infiltration by cancer cells; (2) nutritional deficits such as vitamin B12, folic acid, or iron; (3) hemolysis; (4) myelosuppression secondary to chemotherapy or radiotherapy; (5) toxicity induced by the new antitargeted therapies; (6) low endogenous erythropoietin levels; and (7) anemia of chronic disease, also known as functional iron deficiency (Fig. 15.1). The unexpected finding of low erythropoietin levels in cancer patients by Miller et al. in 1990 [8], together with the toxicity induced by chemotherapy, sets the basis for the use of this agent in cancer patients. Vitamin B12, folic acid, and iron are necessary factors for red blood cell production. Blood loss can be a common association, particularly in colorectal cancer, endometrial cancer (bleeding), or lung cancer (hemoptysis). Anemia can be seen occasionally in cancer patients due to hemolysis secondary to particular chemotherapeutic agents. A short red blood cell half-life has also been reported [9].

Anemia in cancer can also be caused indirectly by the same inflammatory process associated with the disease. In this case, cytokines are produced, with some of them having relevant biological effects with regard to anemia. Two of them, interleukin-1 (IL-1α [alpha], β [beta]) and tumor necrosis factor (TNF-α [alpha]), are known to inhibit the production of erythropoietin by the kidneys. Another important cytokine is IL-6, a proinflammatory factor that acts on the liver to induce the production of hepcidin, a small peptide that has an important role in iron metabolism [10, 11]. It is considered the most important factor in the anemia of chronic disease, also known as functional iron deficiency. Hepcidin induces the degradation of ferroportin, the iron transport protein from the gastrointestinal tract cells or from iron

storage pools in reticuloendothelial cells, mainly macrophages. In other words, hepcidin works in the duodenum, inhibiting the oral absorption of iron, and in the bone marrow, blocking the release of the iron contained in the macrophages. It is understandable that with this scenario, the red blood cells' progenitors lack the two major sources of iron for new red blood cell formation: the gastrointestinal tract, where the enterocytes are unable to absorb either nutritional or therapeutic iron, and the bone marrow, where the macrophages, scavenger cells, do not release the sequestrated iron obtained from the senescent red blood cells [12].

The fact that chemotherapy agents induce anemia is well known. Because dividing cells are targets for these agents, we observed cytotoxicity on cancer cells as well as toxicity in bone marrow cells (myelotoxicity), since most of these cells are in a constant proliferative state. However, we are now facing a quite different scenario in treating cancer since the arrival to our hospital pharmacies of the new targeted agents (tyrosine kinase inhibitors, mTOR inhibitors, monoclonal antibodies, antiangiogenics, etc.). Interestingly, some reports recently published show some of these new agents causing grade 1–2 anemia (range, 15–30%). Among the monoclonal antibodies, trastuzumab has been associated with mild anemia, and bevacizumab has a reduced risk of anemia effect [13–17]. The mechanism(s) of anemia are still unknown for all new targeted agents. Some recent publications established that many of these agents induce by themselves various degrees of fatigue, in some cases quite important, and independently of the level of Hb of the patient.

15.2 The Therapy of Anemia

15.2.1 Red Blood Cell Transfusions

Prior to the introduction of human recombinant epoetins, there were no other treatment options for the correction of anemia than red blood cell transfusions or iron; in many cases, the option was not to give anything. The AIDS epidemic puts blood transfusions under the magnifying glass, and although the safety of our modern blood banks has never been so good, still blood transfusions are associated with unwanted effects. A transfusion of red blood cells causes a sharp increase in Hb level as well as an increase in blood viscosity that varies with the number of units transfused. Interestingly, there has been no large clinical trial to demonstrate an improvement in quality of life after blood transfusions, as has been the case for epoetins.

15.2.2 Erythropoiesis-Stimulating Agents

Human recombinant epoetins were introduced in the early 1990s. Initially there were epoetin alfa and epoetin beta. Both agents are similar to the endogenous molecule, erythropoietin. Ten years later, a new modified erythropoietin molecule was introduced in our pharmacies, darbepoetin alfa. Since the three molecules

Table 15.1 Erythropoiesis-stimulating agents

	Darbepoetin alfa (Aranesp)	Epoetin alfa (Eprex/ Epogen)	Epoetin beta (NeoRecormon)
Indication	Chemotherapy-induced anemia in solid tumors	Chemotherapy-induced anemia in solid tumors, lymphoma, or multiple myeloma	Treatment and prevention of anemia in platinum-based chemotherapy in solid tumors, multiple myeloma, low-grade lymphoma, non-Hodgkin, and chronic lymphocytic leukemia
Bioequivalence	1 μg	200 U	200 U
Preparations/ schedule	150 μg/sc QW = 30,000 U[a]	10,000 U sc/TIW	10,000 U sc/TIW
	500 μg/sc QTW = 100,000 U[a]	30,000 U sc/QW	30,000 U sc/QW
		40,000 U sc/QW	

[a]Approved dose/regimen

stimulate erythropoiesis, they are currently called erythropoiesis-stimulating agents (ESAs) (Table 15.1). Over the last 20 years, more than 20,000 cancer patients with anemia have been enrolled in multiple clinical trials of ESAs to assess the efficacy, side effects, and quality of life. This massive clinical experience with ESAs has demonstrated that they are well tolerated and can effectively increase Hb levels and decrease transfusion use [3–7, 9, 18, 19]. Initially, epoetins were administrated three times weekly following the pattern used for dialysis in chronic renal failure patients. Lately, once-a-week administration has become the most popular schedule. In addition, darbepoetin alfa has an administration schedule of every 3 weeks, besides the once-a-week presentation [20]. In general, ESAs produce significant decreases in transfusion requirements and significant increases in Hb level (around 1 g/dL in 4 weeks), with hematopoietic response rates ranging from 55 to 74% [3–7, 9, 18, 19]. In addition, correction of the anemia by ESAs has been correlated, in a significant way, with improvement in the quality of life of cancer anemic patients. Fatigue is a major symptom of anemia. Cancer-related fatigue has a profound effect on patient quality of life, affecting physical and emotional well-being, as well as relationships with family and friends. The greatest incremental improvement in quality of life occurs when the Hb level increases from 11 to 12 g/dL (range, 11–13 g/dL) [21].

As a result of so many social and medical changes in attitude, anemia management practices have changed over the years. This is reflected by the guidelines for anemia treatment issued first by the American Society of Hematology (ASH) jointly with the American Society of Clinical Oncology (ASCO) [22], by the National Comprehensive Cancer Network (NCCN) [23], and, more recently, by the European Organisation for Research and Treatment of Cancer [24]. The three guidelines strongly recommended ESA treatment for cancer patients with anemia receiving chemotherapy who have a Hb level < 10 g/dL. However, the three guidelines differ somewhat regarding recommendations for treatment of patients with Hb levels of 10–12 g/dL. The correction of anemia should not go over 12 g/dL (Table 15.2) [28].

Table 15.2 Summary of international evidence-based guidelines for treating cancer-induced anemia

Recommendation	ASCO/ASH	NCCN	EORTC [10]	ESMO [25]
Initiate ESA therapy	Hb ≤ 10 g/dL (clinical decision if Hb 10 to ≤12 g/dL)	Hb ≤ 11 g/dL	Hb 9–11 g/dL (clinical decision if Hb ≤ 11.9 g/dL)	Hb ≤ 10 g/dL
Goal of treatment	The lowest Hb concentration needed to avoid transfusions	Maintain Hb between 10 and 12 g/dL	Target Hb should be around 12 g/dL	Hb should not exceed 12 g/dL

Rizzo et al. [26]
NCCN Clinical Practice Guidelines in Oncology [27]

Recently, a new generation of ESA-like agents has been approved by the European Regulatory Agency (EMA). The loss of the patent of the originals has produced a new generation of similar but not identical agents. These are called biosimilars in Europe or follow-on biologics in the United States [29]. Among the biosimilars for anemia, there are already three approved agents: HX575, XM01 (in reality, this agent is an original if one follows its clinical development), and SB309. All these agents receive different trade names in occasions with the same agent. For instance, HX575 has been registered with three different names: Binocrit (Sandoz, Princeton, NJ, USA), Epoetina Hexal (Hexal Biotech, Germany), and Abseamed (Medice Arzneimittel Putter, Germany). Another biosimilar, SB309, has been registered as epoetin zeta, and its trade names are Silapo (STADA, Bad Vilbel, Germany) and Retacrit (Hospira, Warwickshire, UK). The third biosimilar for anemia is epoetin theta. In fact, this agent is an original but generally is included in the biosimilar list, probably owing to the timing of its introduction to the market, the same as the real biosimilars. Its trade name is Eporatio (Ratiopharm-TEVA, Ulm, Germany) [29].

ESAs should be given to patients with chemotherapy-induced anemia to reduce blood transfusions and to increase quality of life. ESAs should not be given when there are other treatable causes of anemia, such as iron deficiency anemia or vitamin deficiencies. ESAs should not be given in radiotherapy when this treatment option is the only anticancer treatment or in anemia associated with cancer in the absence of any active anticancer treatment.

15.2.3 Iron

It is well known that ESAs have a response rate that is suboptimal, ranging from 55 to 74% in most published clinical trials [30]. Several explanations have been found, but in general it is accepted mostly due to functional iron deficiency. The remarkable improvement in the response rate observed with the concomitant administration of intravenous iron to ESAs strongly suggests this possibility. Functional iron deficiency (i.e., lack of bioavailable iron) is a clinical entity where erythropoiesis is impaired owing in part to the sequestration of iron [31] by the macrophages and a blockage of enteral iron absorption mostly mediated by hepcidin [31]. In other words, oral iron is

poorly absorbed or not absorbed at all, and bone marrow iron, although present in the bone marrow, is not available to the making of red blood cells. Parenteral iron therapy has subsequently become an important adjunct to obtaining and maintaining adequate Hb levels in patients with cancer who are receiving chemotherapy. However, despite the good results observed with parenteral iron, many oncologists are still reluctant to use it because of the poor safety profile observed in the past with the old iron preparations, particularly high-molecular-weight dextran (HMWD). The new intravenous preparations (ferric gluconate, ferric carboxymaltose, iron isomaltoside, iron sucrose) show not only a much better safety profile but a much easier administration.

Over the last few years, nine studies on the use of intravenous iron supplementation have been conducted and their results published. In all cases, intravenous iron was delivered concomitantly with ESAs in the treatment of anemia secondary to chemotherapy [32–38]. Except in one study, the study by Steensma et al. [39], all others were favorable to the arm of intravenous iron. In this study, the authors compared parenteral, oral, or no iron supplementation in patients with chemotherapy-associated anemia treated with darbepoetin alfa [39]. Interestingly, the results contrast with the other six other publications [32–38] and two reported clinical trials [40, 41] on the benefits of supplementing iron intravenously in patients receiving a concomitant ESA. It is tempting to posit some potential explanations. The first likely explanation is that the total administered dose of iron seems to be low, approximately 650 mg total [42], compared to the Bastit study [35], which is very similar in design to the Steensma study [39]. In the former, the total iron dose delivered was 400 mg higher [42]. This fact has to do with the design of this study, which planned a total iron dose of 937.5 mg iron, which represents the second lowest dose of iron among the published trials (750–3000 mg). Furthermore, it would be the lowest dose when calculated on a weekly basis (62.5 mg/week). This, by itself, may have limited the potential benefit of intravenous iron supplementation in this particular study.

According to some authors [42, 43], the lack of response to intravenous ferric gluconate in the Steensma study [39] may be attributed to a suboptimal dosing regimen (i.e., a very low average dose but too high single doses) and a high proportion of dropouts rather than a lack of intravenous iron efficacy. In this regard, it is interesting to analyze the results from two recent meta-analyses that confirm the superiority of parenteral intravenous iron over oral or no iron supplementation in terms of better hematopoietic responses and a reduction in blood transfusions [44, 45]. These two meta-analyses had already included data of this trial as presented by Steensma et al. at the 2009 American Society of Hematology (ASH) Congress [46].

Many physicians are still reluctant to incorporate routine use of intravenous iron, largely because of poor understanding and misconceptions of the clinical nature of adverse events reportedly in the past. All of these adverse events were associated with the administration of HMW intravenous iron dextran. Because of that, parenteral iron is therefore underused in oncology patients with anemia. A large body of clinical evidence, with more than 1000 patients evaluated in clinical trials involving the use of intravenous iron, demonstrates an excellent safety profile and a substantial benefit with the new intravenous iron preparations. Interestingly, recently a few publications have reported that intravenous iron sucrose alone was given to patients with gynecological cancer who were receiving chemotherapy; these patients achieved a

higher Hb and hematocrit than the control group [47] and had less transfusion requirements [48] and achieved correction of the anemia with ferric carboxymaltose alone [49]. Further research is required to elucidate a future role for intravenous iron in the management of chemotherapy-induced anemia in cancer patients.

15.3 Side Effects of the Treatments of Anemia

15.3.1 Red Blood Cell Transfusions

Red blood cell transfusions are safer than ever. However, complications from blood transfusions still remain a major concern: infections (viral, bacterial contamination), acute and delayed hemolytic reactions, and acute lung injury are among the most frequent complications. Therefore, blood transfusions are reserved for critical situations but not for mild to moderate degrees of anemia [50]. Recently, some alarm signals have appeared with the use of red blood cell transfusions related to their storage time at the blood bank. Several publications, mainly in the fields of intensive care, cardiology, and trauma, have reported on these complications [51–53]. Most results imply the development of severe complications when blood is older than 2 weeks (see Table 15.3) [56, 57].

Table 15.3 Red blood cell transfusions: risks of complications

Risk factor	Estimated frequency		No. of deaths per million units
	Per million units	Per actual unit	
Infection			
HIV			–
Viral	0.4–0.7	1/1,400,000–1/2,400,000	
Hepatitis A	1	1/1,000,000	0
Hepatitis B	7–32	1/30,000–1/250,000	0–0.14
Hepatitis C	0.6–1.2	1/872,000–1/1,700,000	–
HTLV type I/II	0.5–4	1/250,000–1/2,000,000	0
Parvovirus B19	100	1/10,000	0
Bacterial contamination			
Red cells	2	1/500,000	0.1–0.25
			–
Acute hemolytic reactions	1–4	1/250,000–1/10,000,000	0.67
Delayed hemolytic reactions	1000	1/1000	0.4
Transfusion-related acute lung injury	200	1/5000	0.2
Incorrect transfusions (human error)		1/14,000–19,000	
Red blood cell storage	(1)	(1)	(1)

Modified from Goodnough et al. [54] and Klein et al. [55]
References [50–52]

15.3.2 Erythropoiesis-Stimulating Agents

Over the last 10 years, more than 15,000 patients have participated in clinical trials with different ESAs. The massive clinical experience with these agents has demonstrated that they are well tolerated and safe if used according to registry. Efficacy has been proven in several randomized, placebo-controlled trials [58–62]. These agents decrease the number of blood transfusions and improve the quality of life. All data have been collected and summarized in meta-analysis [63, 64].

15.3.3 Pure Red Cell Anemia

A potential adverse event in the administration of biopharmaceuticals, due to their molecular complexity and their laborious fabrication, is immunogenicity, the possibility of inducing antibody formation. This was the case with epoetin alfa (during the years 1998 and 2003). Only chronic renal patients receiving epoetin alfa were affected [65]. No oncology patients were reported. The condition is called pure red cell anemia (PRCA), and it is caused by antibodies against endogenous erythropoietin. As expected, this medical condition results in no available erythropoietin, associated with severe anemia. The clinical course of antibody-mediated anemia is characterized by a sudden fall in hemoglobin concentration despite ESA therapy, with reticulocyte counts declining to very low levels $< 20 \times 10^9$/L. Affected patients, due to the severity of the anemia, rapidly become transfusion dependent. A bone marrow aspiration shows the absence or near absence of erythroid progenitor cells. The confirmation of PRCA is the detection in the serum of these patients of neutralizing antibodies that not only neutralize the biological activity of the exogenous ESA but also endogenous erythropoietin, thus preventing red cell production in the bone marrow.

PRCA related to ESA therapy is a very rare medical entity, with an exposure-adjusted incidence of 0.02–0.03 per 10,000 patient-years [66]. The peak incidence of PRCA related to ESA therapy occurred during 2002 and 2003, following the report of few cases of chronic renal patients [67]. The cause of this disease has remained elusive, although several factors are believed to have been implicated [65]. The initial most obvious cause was the removal of human serum albumin (HSA) from the epoetin alfa preparation (Eprex, Janssen-Ortho, Toronto, Canada), which was a requirement by the European authorities due to the concern about the transmission of Creutzfeldt-Jakob disease (prions). HSA was replaced by polysorbate 80, and it was initially thought that this vehicle itself might be involved in PRCA development. Another hypothesis is the so-called rubber leachates. The company had introduced a preloaded syringe with a rubber stop. It was not until after the company replaced the rubber stop with one made of Teflon that the cases began to

decrease. A third hypothesis, very plausible at the time, was that it was due to a break in the cold storage chain, which rendered the protein molecule less stable. This fact leads to conformational changes in the tertiary structure of the molecule that was the ultimate cause for its immunogenicity. In total more than 200 cases were reported.

15.3.4 Thromboembolic Events

The use of ESAs has been associated with a higher incidence of thromboembolic events (TEs). In general there is an increased risk of around 1.5–3% [68, 69]. A recent meta-analysis of all randomized, controlled studies of epoetin beta ($n = 12$) [70] evaluated the impact of therapy at different hemoglobin-initiation levels and to different target Hb levels on overall survival, tumor progression, and TEs. An analysis of risk factors predisposing patients to TEs under epoetin beta therapy was also performed. A total of 2297 patients were included in the analysis. The study showed a significantly increased TE rate with epoetin beta compared with control (0.22 events/patient-year vs. 0.14 events/patient-year) and an increased risk of TEs with this agent. These results are consistent with those reported by the meta-analyses of the Cochrane Collaboration [68, 69]. Subgroup analyses based on hemoglobin-initiation level indicate a correlation between hemoglobin-initiation level and risk of TE. This increased TE risk is seen in all of these agents, and it is adequately reflected in the product labeling for all approved ESAs. Among the several risk factors shown for TEs, the most relevant include increasing age (>65), prolonged immobility, malignant disease, multiple trauma, major surgery, previous venous TE, and chronic heart failure [71]. Another meta-analysis to evaluate venous TEs associated with ESA administration reviewed 38 trials including 8172 patients and found a risk rate of 1.57 (CI 95% of 1.31–1.87) [69]. A study-level and patient-level meta-analysis on the benefits and risks of using ESAs in lung cancer patients reported a 10.5% for darbepoetin alfa versus 7.2% for the placebo arm. The study evaluated 9 ($n = 9$) trials with a total of 2342 patients [70]. A recent publication reported an association between RBC and platelet transfusions and an increased risk of TEs and mortality in cancer patients [72]. Interestingly, another recent publication by Fujisaka et al. [73], treating 186 patients with cancer receiving epoetin beta 36,000 IU or placebo weekly for 12 weeks according to the European regulation, showed no significant differences in adverse events; the incidence of TE was 1.1% in both groups. One has to be careful with these data owing to the low number of patients included in this study. A provocative explanation for the high risk for thrombocytosis and venous thromboembolism in cancer patients with chemotherapy-induced anemia has been given recently by Henry et al. [74]. These authors suggest that these events may be related to ESA-induced iron-restricted erythropoiesis, which, interestingly, is reversed by intravenous administration of iron.

Finally, it is worth noting the results of a prospective, multicenter observational study of venous TE in cancer patients receiving chemotherapy. It was observed that those patients with platelet counts $\geq 350{,}000/mm^3$ were associated with a higher

Table 15.4 Adverse effects associated with erythropoiesis-stimulating agents

Thromboembolic events[a]
Arterial hypertension[b]
Pure red cell aplasia[c]
Increased mortality[d]
Stroke[a], seizures[e]
Pain and swelling at the site of administration[f]

[a]RR, 1.67 (1.35–2.06)
[b]0.02–0.03/10,000 patient-years (exposure-adjusted incidence)
[c]Overall survival (OS) HR, 1.08 (CI 95%, 0.99–1.18) [69] and OS HR,1.04 (95% CI, 0.97–1.11) and 1.10 (95% CI, 0.98–1.24) for on-study mortality [63]
[d]≥1/100 to <1/10
[e]≥1/1000 to <1/100
[f]≥1/10

incidence of thrombosis independent of recombinant EPO therapy [75]. These results suggest that a high prechemotherapy platelet count could be a marker to identify patients at risk for venous thrombosis (Table 15.4) [75].

15.3.5 Increased Mortality

In the early 2000s, two publications reported positive clinical outcomes in cancer patients receiving epoetins treated with chemotherapy. One clinical trial used epoetin alfa and the other used darbepoetin alfa; both were compared to a placebo arm [3, 61]. Although both trials did not have survival as an end point, both were highly favorable to the ESA arm in terms of survival. This fact reinforced many old theoretical arguments of the past that suggested that ESAs, by correcting the anemia, would improve tissue oxygenation. As a consequence, tumor tissues would be rendered more sensitive to cancer treatments: radiotherapy and chemotherapy. The follow-up of this rationale was that by maintaining higher Hb levels (higher oxygenation) during the course of the cancer treatment, one should expect better outcomes. This situation led to a series of clinical trials aimed not only at the correction of the anemia but to its prevention. Unfortunately, many of the trials were poorly designed, and soon some of these newly designed clinical trials were showing, unexpectedly, better outcomes in the placebo arm. In particular, the results of two of them showed, for the first time, an association between erythropoietin treatment and increased mortality [76, 77]. The results raised concerns about the safety of ESAs when targeting high Hb levels (13–14 g/dL or higher). A critical analysis of these publications [76, 77] presents serious methodological limitations. The first was an off-label use of epoetin beta using only radiotherapy for head and neck cancer achieving Hb levels of 14–15.5 g/dL and higher, and the second was an anemia-prevention study, also an off-label use, with epoetin alfa in breast cancer patients. The design of these two clinical trials could have confounded the results

and probably influenced the conclusions [78, 79]. In addition, three more studies have been recently published that report a detrimental impact of ESA treatment on survival [80–82]. Many interpretations of these unexpected findings [83, 84] suggest that increased mortality may be because of a higher risk of TEs with the use of ESA therapy. These agents used off label may have caused blood hyperviscosity due to the high hematocrits achieved. Another explanation, very popular until recently, has been that ESAs may promote tumor growth through erythropoietin receptor (EpoR) activation and/or stimulation of angiogenesis [85–88]. This issue has been and still is very controversial due to the detection by some authors [86] of EpoRs on the surface of cancer cells using an anti-EpoR polyclonal antibody (A-20). Some recent publications argue against the validity of these data. One report suggested that the polyclonal antibody (A-20) recognizes heat shock protein-70 (HSP-70) and not the real EpoR. The same authors have identified some genetic homologies between the two molecules [89]. The same authors have published the results on a KO mouse, for EpoR shows staining with the polyclonal antibody A-20 in both the KO mouse and in the control, which clearly suggests nonspecific binding of A-20 [89]. More recently, a monoclonal antibody against the EpoR (A82) [90] has failed to identify any EpoR in 67 human cell lines of different tumor pathologies [91] and in 182 fresh human tissue samples from different patients with different types of cancer [92].

In the last 7 years, there have been an important number of trials on ESAs in cancer patients with a variety of outcomes. As a consequence, several meta-analyses have been performed to bring some light to the field. A meta-analysis published by Bohlius et al. [69] collected the data of 57 trials and 9353 cancer patients. The analysis included randomized, controlled clinical trials on treatment as well as on prophylaxis (off-label) and in cancer patients with anemia without concurrent anticancer treatment (off-label). The effect on overall survival gave an HR of 1.08 (95% CI, 0.99–1.18). In 2009, an individual patient-based meta-analysis was published by Bohlius et al. [63]. The number of patients analyzed was 13,933 from 53 trials. The final outcomes on overall survival resulted in a worse outcome for the patients enrolled in the ESA group (HR, 1.06, 95% CI, 1.00–1.12). On-study mortality HR for the total group of patients was 1.17 (95% CI, 1.06–1.30). Interestingly, for the 10,441 patients who received only chemotherapy, the HR for overall survival was 1.04 (95% CI, 0.97–1.11). In their publication, the authors state that ESAs are safe for chemotherapy-induced anemia. Six other meta-analyses have been performed: five showing a neutral effect of the ESA group (no significant effect on overall survival) [64, 93–96] and one [97] showing a worse overall survival in the group who received ESA.

Ross et al. analyzed 21,378 patients from 49 studies and found no differences in TEs or mortality between the ESA arm and the control arm [93]. Aapro et al. [94] analyzed 1413 patients from 8 studies (epoetin beta, $n = 800$; control, $n = 613$). There was a significantly reduced risk of rapidly progressive disease for epoetin beta (RR 0.78; 95% CI, 0.62, 0.99; $P = 0.042$). Glaspy et al. [64] evaluated 15,323 cancer patients with anemia receiving chemotherapy/radiotherapy, radiotherapy-only treatment, or anemia of cancer receiving no treatment from 60 studies. Results

indicated that ESA use did not significantly affect mortality (60 studies, OR = 1.06; 95% CI, 0.97–1.15) or disease progression (26 studies: OR = 1.01; 95% CI, 0.90–1.14).

In a pooled analysis of individual patient-level data from all randomized, double-blind, placebo-controlled trials of darbepoetin alfa, Ludwig et al. [95] found that this agent did not increase mortality and affected neither progression-free survival nor disease progression. Overall survival and progression-free survival seemed to be better in those patients who achieved Hb >12 or >13 g/dL as compared with those who did not [95]. The same authors investigated the effect of blood transfusions on rates of Hb increase. In the absence of transfusions, the percentage of patients with >1 g/dL in 14 days or >2 g/dL in 28 days increase in Hb was 68.8% for darbepoetin alfa and 52.3% for placebo or 39.1% for darbepoetin alfa and 19.2% for placebo, respectively. Interestingly, the results show that an increase of 1 or 2 g/dL in Hb levels resulting from blood transfusions was associated with an increased risk of death and disease progression. Furthermore, when blood transfusions were excluded from the analysis, the increase in Hb rates was not associated with an increased risk for disease progression or death. In summary, blood transfusions were associated with a greater risk for disease progression and death in both treatment arms and with a greater risk for embolism/thrombosis in the darbepoetin-alfa arm.

More recently, Aapro et al. reported results of an updated meta-analysis of 12 randomized, controlled studies of epoetin beta conducted in 2301 patients undergoing cancer therapy [96], including three recently completed trials with longer-term follow-up in patients with head and neck cancer [76], patients with metastatic breast cancer [98], and patients with cervical cancer [99]. The results of this meta-analysis based on individual patient-level data showed no statistically significant difference between patients receiving epoetin beta and standard treatment in terms of overall survival. In fact, the authors describe a favorable trend with respect to the risk of disease progression for patients receiving this agent [96]. Bennett et al. [97] reported a meta-analysis of phase 3 trials comparing ESAs with placebo or standard of care for the treatment of anemia among patients with cancer. A total of 13,611 patients included in 51 clinical trials were evaluated for survival. Patients with cancer who received ESAs had increased mortality risks (HR = 1.10, 95% CI, 1.01–1.20) than the placebo or the standard of care arm.

Interestingly, over the last few years, several studies have been reported with a major aim being the safety of ESAs. Results show either a neutral clinical outcome or a beneficial one [19, 73, 100–105].

In any event, a major consequence of the safety concerns raised by some studies on ESAs in the treatment of cancer-induced anemia has been the requirement, by the European regulatory authorities, to introduce a warning on the product labels for marketed ESAs to be restricted to a hemoglobin-initiation level <10 g/dL and a Hb target not to exceed 12 g/dL. However, the updated EORTC treatment guidelines recommend the initiation of ESA therapy at Hb levels between 9 and 11 g/dL and the target for treatment with ESAs to achieve a Hb level of ~12 g/dL [106]. ASCO guidelines recommend the initiation of ESA therapy at Hb level < 10 g/dL and to

use ESA to achieve the lowest Hb concentration needed to avoid transfusions [22]. ESMO guidelines also recommend starting ESAs at Hb ≤ 10 g/dL and Hb target not to exceed 12 g/dL (see Table 15.4) [25].

Further research is required to elucidate these still unanswered issues regarding the safety of ESAs for correction of chemotherapy-induced anemia. Two large, multicenter clinical trials with a major aim in survival were initiated few years ago: one in breast cancer using epoetin alfa and the other in lung cancer using darbepoetin alfa. The results from the former were recently published [107]. Interestingly, the primary end point, PFS based on investigator-determined PD, did not meet noninferiority criteria. However, the PFS based on independent review committee-determined PD met noninferiority criteria. For the clinical point of view, the results will not impact in clinical practice. The study in lung cancer is still ongoing until the patient recruitment goal is achieved.

15.3.6 Iron

The old preparations of intravenous iron, particularly high-molecular-weight dextran (HMWD), presented serious adverse effects ranging from allergies to anaphylactic reactions. This is the reason why many oncologists currently are reluctant to use it. The poor safety profile observed in the past with the old iron preparations was well documented. The new intravenous preparations (ferric gluconate, ferric carboxymaltose, iron isomaltoside, iron sucrose) show not only a much better safety profile but a much easier administration. Adverse effects are related to non-transferrin-bound iron (NTBI): toxicity occurs from the release of weakly bound iron. This is what occurred with the old preparations such as HMWD; the new preparations have a very strong iron-binding capacity that translates into much less free iron, the critical point for the serious events of the past, in particular anaphylaxis. The most common adverse effects of the new preparations are back pain, dyspnea, and hypotension [39]. Other adverse effects associated with intravenous iron in the past (e.g., myalgia, pruritus, rash) were not more common than with oral iron or placebo.

In nine published randomized trials, there was no difference in adverse events in the intravenous iron group compared with the no iron or oral iron groups [32–39]. There was no evidence for (1) increased risk of infection, (2) increase in cardiovascular morbidity, or (3) increase in tumor incidence or progression. The incidence of life-threatening adverse events with intravenous iron was <1:700,000 when high MW iron dextran was avoided [108].

Recently, a new preparation of oral iron has been approved (Sucrosomial Iron®)—it is a preparation of ferric pyrophosphate covered by phospholipids plus sucrose esters of fatty acid matrix This allows the molecule to be absorbed by the gastrointestinal tract independently of hepcidin and as such to get absorbed by cancer patients. Since it is a sort of liposomal iron, this does not causes the common side effects associated to oral iron. A recent publication [109] shows that Sucrosomial Iron® (Sideral®) is significantly more bioavailable than microencapsulated ferric pyrophosphate ingredients, Lipofer® and Sunactive®, and ferrous sulfate in a Caco-2 cell model.

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Bone Marrow Toxicity: White Blood Cells

16

Matti S. Aapro

Abstract

Chemotherapy-induced febrile neutropenia (FN) may lead to dose reductions and/or delays that may decrease the chances of curative or life-prolonging treatment in patients with chemo-responsive tumors and is related to increased patient mortality. While often associated with a need for hospitalization, this complication can also be treated in an outpatient setting in low-risk patients. Prophylactic treatment with granulocyte colony-stimulating factors (G-CSFs), such as filgrastim (including approved biosimilars and tbo-filgrastim), lenograstim, or pegfilgrastim and lipegfilgrastim, is available to reduce the risk of chemotherapy-induced neutropenia and its consequences, according to the European Society of Medical Oncology (ESMO) and European Organisation for Research and Treatment of Cancer (EORTC) and other guidelines. Prophylactic G-CSF is recommended in patients receiving a chemotherapy regimen with a risk of FN above 20%. Patient-related risk factors (in particular, older age [≥65 years]) may increase the overall risk of FN and need to be evaluated to decide the use of prophylaxis for regimens with intermediate (10–20%) risk of FN.

Keywords

Granulocyte colony-stimulating factor · Filgrastim and tbo-filgrastim · Lenograstim · Pegfilgrastim · Lipegfilgrastim · Biosimilars · Neutropenia · Febrile neutropenia · Chemotherapy · Guidelines · EORTC · ESMO

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M. A. Dicato, E. Van Cutsem (eds.), *Side Effects of Medical Cancer Therapy*,
https://doi.org/10.1007/978-3-319-70253-7_16

16.1 Introduction

Chemotherapy-induced febrile neutropenia (FN) with infection may increase patient mortality, and both FN and mortality risk can be prevented with appropriate use of granulocyte colony-stimulating factors (G-CSFs) [1]. Febrile neutropenia is seen most often during the first cycle of myelosuppressive therapy and has been documented to occur in 287/2692 (10.7%) of adult cancer patients during the first 3 cycles of chemotherapy [2]. Prevention of FN reduces emergency hospital admissions, antibiotic usage, and the need for dose reductions or delays in chemotherapy administration, which are associated with a poorer cancer outcome, at least in curative settings [3].

In 2010, a guidelines working party of the European Organisation for Research and Treatment of Cancer (EORTC) systematically reviewed available published data and derived evidence-based recommendations on the appropriate use of G-CSF in adult patients receiving chemotherapy [4]. These recommendations are very similar to those of other groups like the updated American Society of Clinical Oncology (ASCO) guidelines [5] and the recent European Society for Medical Oncology (ESMO) clinical practice guidelines [6].

This chapter will discuss the topic using the six recommendations put forward by the EORTC guidelines and update them [4].

16.2 Definition of Febrile Neutropenia and Complication Risk Assessment

Febrile neutropenia is often defined as an absolute neutrophil count (ANC) of $<0.5 \times 10^9$/L or $<1.0 \times 10^9$/L predicted to fall below 0.5×10^9/L within 48 h, with fever or clinical signs of sepsis. Currently, ESMO defines fever in this setting as a rise in oral temperature to >38.3 °C sustained for at least 1 h. It is suggested that therapy be initiated if a temperature of >38.0 °C is present for at least 2 h or a reading of >38.3 °C is obtained on a single occasion [6].

Recognizing patients at risk for complications of FN is of major importance in that it determines the possibility of outpatient versus inpatient management of the event. This can be achieved using risk indices, and one of these has been developed by the Multinational Association of Supportive Care in Cancer (MASCC) (Table 16.1) [7]. According to the MASCC score, patients with a score of 21 or more points are considered at low risk, while all other patients are considered at high risk of infectious complications.

16.3 Side Effects and Precautions for Use of G-CSF

Bone, joint, or muscle pain is a common (20% incidence) adverse event associated with G-CSF treatment, occurring with much the same frequency whether the agent is pegylated or not. It is generally easy to manage with standard analgesics. Leukocytosis (white blood cell count $>100 \times 10^9$/L) after G-CSF administration has been rarely observed and does not occur more frequently with pegfilgrastim.

Table 16.1 Score derived from the logistic equation of the Multinational Association of Supportive Care in Cancer (MASCC) predictive model (1386 patients with FN)

Determinant	Points
Burden of illness	
No or mild symptoms	5
Moderate symptoms	3
No hypotension	5
No chronic obstructive pulmonary disease	4
Solid tumor or no previous fungal infection in hematologic cancer	4
Outpatient status	3
No dehydration	3
Age <60 years	2
Threshold: score ≥21 (maximum 26) predicting less than 5% of severe complications	

Adapted from [7]

G-CSFs can induce elevation of cancer antigen 15–3, which is used for monitoring breast cancers [8].

G-CSF usage is not indicated during chemoradiotherapy to the chest according to ESMO [6], and even without chest radiation according to ASCO [5], owing to an increased risk of complications and death, and there is also a risk of worsening thrombocytopenia when such agents are given immediately before or simultaneously with chemotherapy.

16.4 Is There a Risk of Leukemia Related to G-CSF Usage?

Since the development of G-CSF, there has been a debate about the potential leukemogenic risk of the product.

The Surveillance, Epidemiology, and End Results (SEER) analysis of patients with breast cancer aged ≥65 years reported an incidence of myelodysplastic syndrome (MDS)/acute myeloid leukemia (AML) of 1.77% among 906 patients receiving growth factor support compared with 1.04% among the 4604 patients not receiving colony-stimulating factors. One has to note that patients receiving growth factor tended to have positive lymph nodes and received either more intense radiation therapy or high-dose cyclophosphamide treatment [9]. These findings did raise concern that G-CSF use in a high-dose setting among breast cancer patients could be associated with a high risk of secondary MDS or AML. The report of a US registry data analysis has shown that the overall risk is small, even among elderly patients [10].

A meta-analysis of randomized, controlled trials has shown that there is a modestly increased risk of AML/MDS (approximately 4 per 1000 cases) associated with the use of particular chemotherapy schedules in combination with G-CSF support. Notably a significant increase in risk of AML/MDS was observed where G-CSF support was associated with a greater total dose of chemotherapy (Mantel-Haenszel relative risk [RR] = 2.334, $P = 0.009$) but not when the planned total dose of chemotherapy with G-CSF was the same in each study arm, such as dose-dense

schedules. Furthermore, all-cause mortality was decreased in patients receiving chemotherapy with G-CSF support. Greater reductions in mortality were observed with greater chemotherapy dose intensity [1].

Available data do not support an association between G-CSF administration to healthy donors and the occurrence of G-CSF-induced malignant transformation. An important report concerns 2408 unrelated PBSC donors prospectively evaluated by the National Marrow Donor Program (NMDP) between 1999 and 2004. Six percent of donors experienced grade III–IV CALGB toxicities, and 0.6% experienced toxicities that were considered serious and unexpected. Complete recovery was universal, however, and no late adverse events (AEs) attributable to donation have been identified. The authors concluded that peripheral blood stem cell collection in unrelated donors is generally safe, but nearly all donors will experience bone pain, one in four will have significant headache, nausea, or citrate toxicity, and a small percentage will experience serious short-term AEs [11].

16.5 Why Not Use Antibiotics to Prevent Febrile Neutropenia?

The use of antibiotic prophylaxis to prevent infection and infection-related complications in cancer patients at risk of neutropenia is not recommended by the EORTC or ESMO or ASCO guidelines. There was some suggestion of benefit in some analyses [12, 13], but other groups discuss that the presently available evidence is too limited to allow conclusions to be drawn regarding the relative merits of antibiotic versus CSF primary prophylaxis [14–16].

In one study the ciprofloxacin antibiotic prophylaxis was without efficacy against FN in patients with breast cancer treated with docetaxel-based therapy, but some benefit is observed when it is added to pegfilgrastim [17]. The recommendation 1 of the EORTC working party takes into account the finding that, in randomized controlled trials in patients receiving chemotherapy, routine fluoroquinolone prophylaxis has been shown to lead to an increase in resistance among gram-positive and gram-negative isolates compared with non-prophylaxed controls [13]. The clinical consequences of resistance development are a major concern nowadays, and it is important to avoid unwarranted use of antibiotics to lower the risk of drug resistance.

Finally, one may mention the potential benefit of G-CSF, which may help prevent or treat mucositis and stomatitis and decrease diarrhea in some studies [17–19].

16.5.1 EORTC Recommendation 1: Patient-Related Risk Factors for Increased Incidence of FN

Patient-related risk factors should be evaluated in the overall assessment of FN risk before administering each cycle of chemotherapy. Particular consideration should be given to the elevated risk of FN for elderly patients (aged 65 and over). Other adverse risk factors that may influence FN risk include advanced stage of disease,

experience of previous episode(s) of FN, lack of G-CSF use, and absence of antibiotic prophylaxis. However, please note that the indiscriminate use of antibiotic prophylaxis for patients undergoing treatment for solid tumors or lymphoma is not recommended, either by this working party or the EORTC Infectious Disease Group (*recommendation grade*: *B*) [4].

16.5.1.1 Discussing EORTC Recommendation 1: Patient-Related Risk Factors for Increased Incidence of FN and Complications of FN

Older age (particularly ≥65 years) is the patient-related factor most consistently associated with an increase in FN risk, and this patient group consistently benefits from G-CSF prophylaxis [20].

Several investigators have developed models for predicting neutropenia based on the current risk factors. Such models may prove to be invaluable clinical tools. A study has been performed to develop and validate a risk model for neutropenic complications in cancer patients receiving chemotherapy. The study population consisted of 3760 patients with common solid tumors or malignant lymphoma who were beginning a new chemotherapy regimen. The risk of neutropenic complications was confirmed to be greatest in cycle 1. After adjustment for cancer type and age, major independent risk factors in multivariate analysis included prior chemotherapy, abnormal hepatic and renal function, low white blood count, chemotherapy, and planned delivery greater than 85% [21].

16.5.2 EORTC Recommendation 2: Chemotherapy Regimens Associated with Increased Risk of FN

Consideration should be given to the elevated risk of FN when using certain chemotherapy regimens, (*recommendation grade*: *A/B* (depending on the evidence for each chemotherapy regimen)). It should be noted that this list is not comprehensive and there may be other drugs or regimens associated with an increased risk of FN [4].

16.5.2.1 Discussing EORTC Recommendation 2: Chemotherapy Regimens Associated with Increased Risk of FN

The literature review by the EORTC committee provides a listing of chemotherapy regimens, which helps clinicians when evaluating the need for prophylactic intervention. Updated listings are available with ASCO and NCCN guidelines. An important consideration is that targeted agents may exacerbate the risk of myelosuppression. One has to consider that for many regimens the reporting of FN has been done with different definitions of FN and in many cases may be underestimated. It is also important to realize that patients admitted to protocols are subject to screening and various inclusion/exclusion criteria and therefore often in a better general status than usual patients. Thus, the risk of FN is probably higher than that observed in the study report. Finally, very often the use of prophylactic antibiotics or even G-CSF is not mentioned in the published papers.

16.5.3 EORTC Recommendation 3: G-CSF to Support Chemotherapy

In situations where dose-dense or dose-intense chemotherapy strategies have survival benefits, prophylactic G-CSF should be used as a supportive treatment (*recommendation grade*: *A*).

If reductions in chemotherapy dose intensity or density are known to be associated with a poor prognosis, primary G-CSF prophylaxis should be used to maintain chemotherapy. Examples of this could be when the patient is receiving adjuvant or potentially curative treatment or when the treatment intent is to prolong survival (*recommendation grade*: *A*). Where treatment intent is palliative, the use of less myelosuppressive chemotherapy or dose/schedule modification should be considered (*recommendation grade*: *B*) [4].

16.5.3.1 Discussing EORTC Recommendation 3: G-CSF to Support Intensive Chemotherapy Regimens

Intensification of chemotherapy regimens with dose-dense (increased frequency) or dose-intense (increased dose) chemotherapy is increasingly used and has been shown in some situations to improve long-term clinical outcomes. Multiple studies have indicated that, because the time to neutrophil recovery is around 12 days, pegfilgrastim can be safely administered after chemotherapy in patients receiving treatment at 14-day intervals, as demonstrated in a breast cancer study [22].

Benefits of growth factor administration to maintain intended dose frequency and intensity have been confirmed by a level I meta-analysis of nine randomized controlled trials (seven with G-CSF) in the setting of malignant lymphoma. Eight of the trials showed better dose intensity in the growth factor arm than in the control arm [23].

In another meta-analysis by Kuderer et al., ten trials were identified that used relative dose intensity (RDI) as an outcome. The average RDI among control patients ranged from 71.0 to 95.0%, with a mean of 86.7%. Among G-CSF-treated patients, the average RDI ranged from 91.0 to 99.0%, with a mean of 95.1%. None of the 10 G-CSF treatment arms reported a mean RDI of <90%, whereas six of ten control groups reported a mean RDI of <90%, with four control arms averaging an RDI of ≤85%. This represents an 8.4% increase in dose intensity. Average RDI was significantly higher in patients who received G-CSF compared with control patients ($P < 0.001$) [24].

The lack of evidence that dose modifications decrease the benefit of palliative treatments has led the EORTC group not to recommend the use of growth factors to sustain such regimens.

16.5.4 EORTC Recommendation 4: Impact of the Overall FN Risk on G-CSF Use

The risk of complications related to FN should be assessed individually for each patient *at the beginning of each cycle*. When assessing FN risk, the clinician should take into account patient-related risk factors (recommendation 1), the chemotherapy regimen and associated complications (recommendations 2 and 3), and treatment

intent (recommendation 3). Prophylactic G-CSF is recommended when there is ≥20% overall risk of FN. When chemotherapy regimens associated with an FN risk of 10–20%, particular attention should be given to the assessment of patient characteristics that may increase the overall risk of FN (*recommendation grade*: *A*) [4].

16.5.4.1 Discussing EORTC Recommendation 4: Impact of the Overall FN Risk on G-CSF Use

There is strong evidence supporting the use of G-CSF to prevent FN coming from three level I meta-analyses. It should, however, be noted that while the meta-analyses support the use of G-CSF to reduce FN, some individual studies included in these publications did not [23–25].

In the lymphoma meta-analysis, with four studies analyzed, the underlying risk of FN (neutrophils below 1.0×10^9/L) was at least 36%, and RR reduction with G-CSF was approximately 26% (RR 0.74; 95% CI 0.62, 0.89). In a review of solid tumors, the underlying FN risk was approximately 50%, and RR reduction with G-CSF was approximately 50%. In the largest comprehensive meta-analysis of patients with lymphoma or solid tumors across 15 randomized controlled trials (9 trials with filgrastim, 5 with lenograstim, and 1 with pegfilgrastim), in which the overall underlying risk of FN was 37%, the RR reduction with G-CSF was 46% (RR 0.54; 95% CI 0.43, 0.67; $P \leq 0.001$) [24].

In summary, recommendations 1–3 of the EORTC identify a number of factors that should influence the clinician when considering primary prophylactic G-CSF for patients scheduled to receive chemotherapy. Each of these factors should be incorporated into an assessment of the overall risk of FN for each patient on an individual, case-by-case basis.

16.5.5 EORTC Recommendation 5: G-CSF in Patients with Existing FN

Treatment with G-CSF for patients with solid tumors and malignant lymphoma and ongoing FN is indicated only in special situations. These are limited to those patients who are not responding to appropriate antibiotic management and who are developing life-threatening infectious complications (such as severe sepsis or septic shock) (*recommendation grade*: *B*) [4].

16.5.5.1 Discussing EORTC Recommendation 5: G-CSF in Patients with Existing FN

There are no large randomized studies about the use of growth factors in patients with existing FN. One meta-analysis has presented evidence that when G-CSF or GM-CSF is used therapeutically in conjunction with standard therapy (intravenous antibiotics and other supportive care) for patients with ongoing FN, there is a marginal but statistically significant improvement in FN-related events compared with standard treatment alone [26]. The authors of this meta-analysis do, however, indicate that this result requires further investigation as the analysis was not adequately powered to observe the impact of CSF use in patients with ongoing FN.

The EORTC recommendations are similar to those of ASCO and err on the side of caution, as it is clearly preferable to administer a drug that can enhance the activity and production of leukocytes in a situation of high risk for the patient.

16.5.6 EORTC Recommendation 6: Choice of Formulation

Filgrastim, lenograstim, and pegfilgrastim have clinical efficacy, and we recommend the use of any of these agents, according to current administration guidelines, to prevent FN and FN-related complications, where indicated. Filgrastim biosimilars are now also a treatment option in Europe (*recommendation grade*: *A*) [4].

16.5.6.1 Discussing EORTC Recommendation 6: Choice of Formulation

The EORTC guidelines do not suggest a preference for the type of G-CSF. Two biosimilars to daily filgrastim have been approved in Europe and are marketed by various companies using different trade names: Ratiograstim (filgrastim; XM02), Filgrastim Ratiopharm, Ratiopharm GmbH; Biograstim (filgrastim; XM02), CT Arzneimittel GmbH; Tevagrastim (filgrastim; XM02), Teva Generics GmbH; filgrastim Zarzio (EP2006), Sandoz GmbH; and filgrastim Hexal (EP2006), Hexal Biotech Forschungs GmbH.

The guidelines indicate that because biosimilar products are not generic products, a switch from filgrastim to a biosimilar is considered a change in clinical management. To ensure traceability and thus robust pharmacovigilance, clinicians are encouraged to identify a product by brand name and ensure that no changes in treatment are made without informing both physician and patient. We have discussed elsewhere about biosimilars [27] and the stringent criteria under which the products recognized by the European Medicines Agency are produced and alluded to the lower cost of biosimilars that should allow clinicians to adhere to international guidelines [28]. Of note, tbo-filgrastim is not technically a biosimilar [29].

Unlike daily G-CSF, pegfilgrastim is not eliminated rapidly, and rates of turnover are regulated by neutrophil level. Active levels of pegfilgrastim persist for approximately 14 days or until neutrophil recovery is achieved. Several studies suggest that pegfilgrastim might achieve a better protection from febrile neutropenia than filgrastim, and meta-analyses confirm this impression [30]. Certainly the once-per-cycle administration of pegfilgrastim can be of importance in many clinical settings. After publication of those guidelines, another long-acting agent (lipegfilgrastim) has been developed and approved for use by several registration authorities. It has some differences with pegfilgrastim which have probably no clinical significance [31]. The EORTC guidelines group has commented that except for one study the superiority of pegfilgrastim was seen when filgrastim was

used for a relatively short 5–7-day period, which does not comply with current guidelines. ESMO recommendations state that administration of daily G-CSF should start 24–72 h after chemotherapy and continue until ANC recovery, which typically takes 10–11 days [6].

16.6 Summary

In conclusion, the EORTC working party has produced up-to-date recommendations for G-CSF use that are relevant to current European clinical practice, as summarized in Fig. 16.1. Such guidance, taken into account by recent ESMO clinical practice guideline [6], should improve patient management strategies in oncology across Europe. There are, however, still many areas where guidelines committees lack sufficient level I supportive evidence to clarify some recommendations, as discussed in this chapter. In addition, let us indicate that G-CSFs have not been discussed in this chapter in pediatric indications or some hematological malignancies, nor the topic discussed by ASCO on the management of patients exposed to lethal doses of total-body radiotherapy, but not doses high enough to lead to certain death resulting from injury to other organs. In this setting one should include the prompt administration of CSFs or pegylated granulocyte CSFs [5].

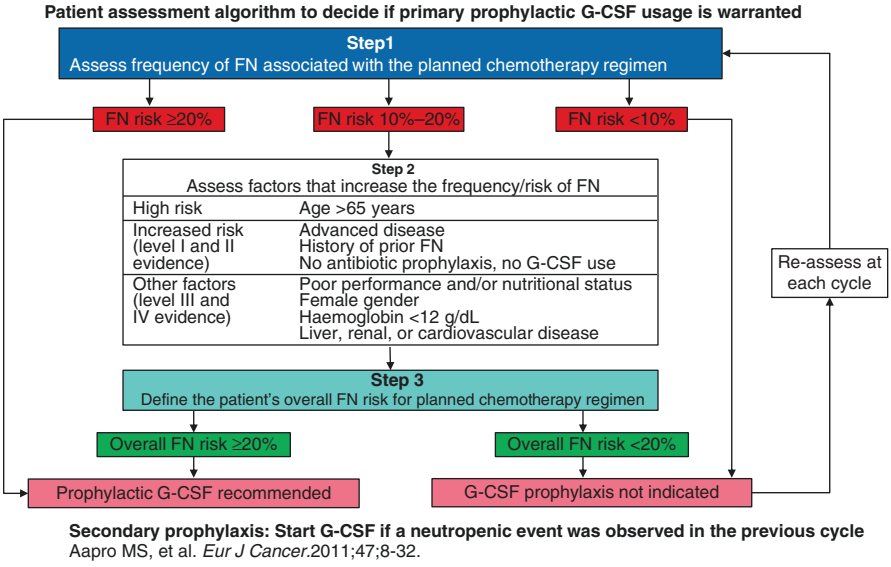

Fig. 16.1 EORTC patient assessment algorithm to decide primary prophylactic G-CSF usage. *FN* febrile neutropenia, *G-CSF* granulocyte colony-stimulating factor (adapted from Aapro et al. [4], Copyright 2011, with permission from Pergamon)

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Toxicity of Bone-Targeted Agents in Malignancy

17

Caroline Wilson, Fiona Taylor, and Robert Coleman

Abstract

The bisphosphonates have been in clinical use for three decades. During this time the adverse event profile and favorable risk-benefit ratio have become clearly defined and strategies identified for minimizing the impact of these side effects on patients. More recently, denosumab has been incorporated into clinical practice and so far demonstrated mild and treatable side effects. Long-term adverse events are infrequent but merit special attention.

In this chapter we review the side effects of the four bisphosphonates licensed for use in malignancy, including clodronate, ibandronate, pamidronate, and zoledronic acid as well as the new targeted agent, denosumab.

Keywords

Bisphosphonates · Zoledronic acid · Denosumab · Toxicity · Acute phase reactions · Renal impairment · Osteonecrosis of the jaw · Atypical femoral fracture

17.1 Introduction

Bone metastasis is a common feature of many tumor types including those arising in the breast, prostate, kidney, lung, and multiple myeloma. Metastasis to bone can lead to skeletal-related events (SRE) including hypercalcemia of malignancy, spinal cord compression, pathological fracture, and surgery to bone, thus adversely affecting quality of life of patients with advanced malignancy [1].

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M. A. Dicato, E. Van Cutsem (eds.), *Side Effects of Medical Cancer Therapy*,
https://doi.org/10.1007/978-3-319-70253-7_17

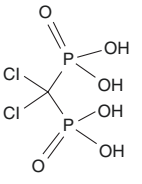
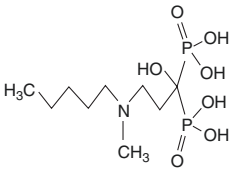
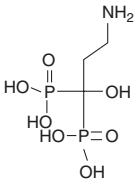
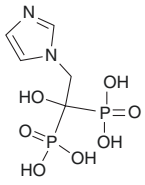
Therapies targeting bone metastasis have been a focus of research and development over the past three decades. These include the bone matrix homing bisphosphonates that are taken up during osteoclast bone resorption, and the more recently developed RANK ligand inhibitor, denosumab, which prevents the activation of osteoclasts. Inhibition of osteoclast activity strengthens bone, thus largely preventing the devastating complications associated with bone metastasis.

17.2 Bisphosphonates

17.2.1 Clinical Indications and Pharmacology

Bisphosphonates are effective in the treatment of established metastatic bone disease and the prevention of skeletal-related events including hypercalcemia of malignancy, spinal cord compression, pathological fracture, and surgery to bone. Four bisphosphonates are currently approved for use in malignancy-associated metastatic bone disease in Europe and include oral clodronate, oral or intravenous ibandronic acid, intravenous pamidronate, and zoledronic acid [2]. Only pamidronate and zoledronic acid are approved in the oncology setting within the United States (see Table 17.1).

Table 17.1 Summary of approved bisphosphonates for use in malignancy

	Clodronate	Ibandronate	Pamidronate	Zoledronate
Dose (mg)	1600–3200	6 50	90	4
Route of administration	Oral	IV Oral	IV	IV
Frequency of administration	Twice daily	3–4 weeks Daily	3–4 weeks	3–4 weeks
Chemical structure				
Launched indications	Bone metastasis Hypercalcemia of malignancy	Bone metastasis Hypercalcemia of malignancy	Bone metastasis Bone cancer Hypercalcemia of malignancy	Bone metastasis Bone cancer Hypercalcemia of malignancy
Relative potency[a]	1	100	1000	>10,000
Pivotal trials (references)	[27, 39, 89–91]	[40, 41, 92]	[93–95]	[30, 31, 35, 96]

Chemical structure reproduced from medicines complete.com

[a]Dose response for the inhibition of 1,25-(OH)2 vitamin D3-induced hypercalcemia in thyroparathyroidectomized rats (120)

Bisphosphonates have also been used in the adjuvant setting to prevent bone loss associated with anticancer therapy. The bisphosphonates used in this setting also include alendronate, etidronate, and risedronate. None of the bisphosphonates have been FDA labeled for this use but remain approved for the treatment of osteoporosis in high-risk populations, and as such their use has been extrapolated to patients at high risk of bone loss during anticancer therapy. The evidence supporting the use of bisphosphonates for prevention of metastasis in postmenopausal women with breast cancer is now clear [3], but remains an ongoing area of controversy.

Bisphosphonates are stable synthetic analogues of pyrophosphate with a P-C-P backbone and an R_1 side chain that acts as a "bone hook" resulting in avid binding to the bone surface. There are two main classes of bisphosphonates: aminobisphosphonates that contain an R_2 covalently bonded nitrogen atom, i.e., zoledronic acid, pamidronate, and ibandronic acid, and non-nitrogen-containing compounds such as clodronate. The mechanisms of action of these two classes are different; nitrogen-containing bisphosphonates inhibit farnesyl diphosphate synthase in the mevalonate pathway leading to a reduction in signaling GTPases, while non-nitrogen-containing bisphosphonates are metabolized to hydrolysis-resistant ATP analogues [4].

Bisphosphonates are taken up by osteoclasts during bone resorption and result in osteoclast apoptosis and thus reduced bone turnover. Their bioavailability is determined by the route of administration, with poor absorption (0.5–3%) when given by mouth. Following intravenous administration, the half-life in serum is less than 1 h, with approximately 30–60% of the infused dose rapidly binding to the bone surface and the remainder excreted by the kidney. The half-life in bone is however substantially longer and measurable in years, with evidence of ongoing biological activity after a single infusion of 4 mg for >3 years [5].

17.2.2 Animal Toxicology and Teratogenicity

17.2.2.1 Animal Studies

Bisphosphonates are excreted in a non-metabolized form in the kidneys of mammals. Preclinical studies in rats demonstrated that the renal toxicity is not only linked to renal excretion rates but also varies according to the particular bisphosphonate. A comparison of ibandronic acid 10–20 mg/kg, zoledronic acid 3–10 mg/kg, and intraperitoneal clodronate injection 200 mg/kg twice daily demonstrated tubular degeneration and single cell necrosis of proximal convoluted tubules on the fourth day of dosing, with zoledronic acid showing the strongest dose-effect relationship [6]. These data were further supported in a rat model using clinically relevant doses of zoledronic acid (1 mg/kg or 3 mg/kg) and ibandronic acid (1 mg/kg). The rats were treated on a single infusion protocol or an intermittent intravenous dosing protocol every 3 weeks. Ibandronic acid induced similar proximal tubular damage in both dosing protocols; however, zoledronic acid demonstrated increased renal toxicity at the intermittent dosing versus the single dose. Thus the cumulative use of zoledronic acid appears to increase toxicity in rats, but ibandronic acid may have a safer profile when used repeatedly [7]. The longer renal half-life of

zoledronic acid (150–200 days) compared to ibandronic acid (24 days) may explain the differences in cumulative toxicity since zoledronic acid will take longer to excrete [8].

Bisphosphonates have been associated with various adverse reproductive toxicities in animal studies, including dystocia, teeth abnormalities, visceral anomalies, and failure of embryo implantation. As such they are contraindicated during pregnancy. However, their use in humans has been generally reassuring [9]. In a review of 15 articles describing the use of bisphosphonate during pregnancy that included 65 mother-child pairs, no skeletal or congenital abnormalities were reported. Adverse outcomes possibly attributable to bisphosphonate use included marginal decreases in gestational gen and birth weight and transient neonatal electrolyte abnormalities; however, no long-term health consequences were reported in any infant. Furthermore, the outcome of 21 pregnancies exposed to first trimester bisphosphonates compared to matched control subjects did not demonstrate any adverse events in the pregnancy, suggesting bisphosphonates may not pose a significant teratogenic risk in humans [10]. The balance of risks to the pregnancy, with consideration of the potential teratogenic risk in humans, must always be weighed against the benefits of bisphosphonate treatment.

Post partum, there is evidence, in vivo, of passage of bisphosphonates into milk, and thus it is recommended that their use during breastfeeding should be avoided. A clinical case report of intravenous monthly pamidronate use during breastfeeding did not demonstrate pamidronate in breast milk collected for 48 h after the first infusion, suggesting pamidronate may be safe during lactation in humans [11].

17.2.3 Systemic Acute Effects

17.2.3.1 Acute Phase Response

The acute phase response is a systemic inflammatory reaction characterized by flu-like symptoms including fever, arthralgia, myalgia, exhaustion, and leukocytosis. These reactions have most commonly been described with the intravenous bisphosphonates, zoledronic acid, ibandronic acid, and pamidronate. They occur more commonly after the first infusion, and symptoms dissipate with subsequent infusions. Treatment involves paracetamol and nonsteroidal anti-inflammatory agents. All components of the acute phase response have a peak onset within 1 day with a median duration of 3 days. Severity is mild to moderate in 90% of cases [12] and self-limiting in nature.

The cause of the acute phase reaction is thought to be due to a transient increase in gamma/delta (γ/Δ) T lymphocytes and release of tumor necrosis factor alpha and interleukin-6 following the use of an aminobisphosphonate [13, 14]. The acute phase response is associated with long-term effects on white cells with reductions persisting for a year in patients who experienced the acute phase response, not only in γ/ΔT, but also in total lymphocytes and eosinophils [15].

The incidence of the acute phase response appears to be similar between intravenous bisphosphonates. In breast cancer and myeloma patients treated with

zoledronic acid or pamidronate, the frequency of fever was 38% vs 31%, respectively [16]. When zoledronic acid (4 mg every 4 weeks) was compared to oral ibandronic acid (50 mg daily) in a phase III trial of breast cancer patients, fever expectedly occurred more frequently in the zoledronic acid group (16.8% zoledronic acid vs 0% oral ibandronic acid) [17]. However, intravenous ibandronic acid is associated with the acute phase reaction, although at a lower frequency than zoledronic acid, [18] indicating that the incidence of the acute phase reaction may be more dependent on the route of administration than the specific type of aminobisphosphonate. The incidence of acute phase reactions may be less common in immunocompromised cancer patients than in healthy subjects or patients with malignancy who do not have metastasis [20].

17.2.3.2 Metabolic

Prolonged use of bisphosphonates can be associated with alterations in calcium, magnesium, phosphate, and vitamin D metabolism. Hypocalcemia is the most commonly reported metabolic side effect of bisphosphonates. In studies of bisphosphonates, without calcium and vitamin D supplementation, the incidence of hypocalcemia compared to placebo was greater with zoledronic acid (39% vs 7%) [20], but only slightly higher than placebo with ibandronic acid, pamidronate, and clodronate [21]. Concomitant use of oral calcium and vitamin D supplements is recommended as routine with zoledronic acid and advised for ibandronic acid or pamidronate if dietary intake and sunlight exposure are felt to be insufficient, both of which are common in cancer patients [22].

The severity of hypocalcemia is usually mild and often subclinical, although persistent severe hypocalcemia occasionally occurs. There are recognized exacerbating factors such as renal impairment, concurrent use of aminoglycosides which can lower calcium and magnesium, preexisting vitamin D deficiency, hypomagnesemia, and hypoparathyroidism [23]. In an exploratory study comparing changes in bone biochemistry in metastatic breast cancer patients on prolonged bisphosphonate therapy compared to healthy controls matched for age, gender, and renal function, bisphosphonate use was associated with elevated PTH (5.7 vs 4.8 p mol/L $p = 0.043$) when serum calcium was at the lower range. Sixty-two percent of patients demonstrated a suboptimal level of vitamin D, and 18% were deficient in 25-hydroxy vitamin D despite supplementation with 400 IU of vitamin D daily [24].

Hypomagnesemia, hypokalemia, and hypophosphatemia have all been described with zoledronic acid but are less common than hypocalcemia.

17.2.3.3 Renal Toxicity

Rat models indicated that proximal tubular necrosis was the predominant mechanism of renal injury associated with several bisphosphonates. However in clinical studies, different bisphosphonates demonstrate distinctive patterns of renal damage. Zoledronic acid induced renal toxicity is characterized by acute tubular necrosis and apoptosis [25]. Pamidronate, however, may induce a collapsing focal segmental glomerulosclerosis [26].

Table 17.2 Recommended dosing and schedule of bisphosphonates according to creatinine clearance

Bisphosphonate	Baseline creatinine clearance (mL/min)	Recommended dose in malignant bone disease (infusion time)
Clodronate	>30	1600 mg daily
	10–30	800 mg daily
	<10	Not recommended
Ibandronate	>50	6 mg q3–4 weeks (15 min)
	≥30	4 mg q3–4 weeks (1 h)
	<30	2 mg q3–4 weeks (1 h)
Pamidronate	≥30	90 mg q3–4 weeks (1.5–4 h dependent on creatinine)
	<30	Not recommended
Zoledronate	>60	4 mg q3–4 weeks
	50–60	3.5 mg q3–4 weeks
	40–49	3.3 mg q3–4 weeks
	30–39	3 mg q3–4 weeks
	<30	Not recommended

Toxicity is dependent on both dose, scheduling and, for intravenous preparations, the infusion rates (see Table 17.2). Oral bisphosphonates have not been demonstrated to cause clinically relevant renal impairment in human studies. Clodronate had a similar rate of renal impairment to that of placebo in breast cancer [27]. Renal adverse events with ibandronic acid (6 mg via a 1–2 h infusion 3–4 weekly) in metastatic breast cancer appear to be similar in frequency to placebo-treated patients (4.5% ibandronic acid vs 4% placebo). Pamidronate, at doses higher than 90 mg, may cause renal impairment [28], although this may also occasionally occur at standard doses [29].

Early dose-finding studies with zoledronic acid use in metastatic bone disease suggested an 8 mg or 4 mg dose infused over 5 min was efficacious, and this dose was taken forward into phase III trials. However, a dose- and schedule-dependent effect on renal function was seen which resulted in the abandonment of the 8 mg dose and lengthening of infusion time to 15 min. With the 4 mg dose and longer infusion time, the phase III randomized trials of zoledronic acid in prostate, breast, myeloma, and lung cancer patients demonstrated the incidence of renal impairment to be ~10–15% (as defined by an increase in serum creatinine of ≥0.5 mg/dL [if baseline <1.4 mg/dL] or 1.0 mg/dL [if baseline ≥1.4 mg/dL] and an increase in GFR ≥25% from baseline). This incidence was not dissimilar to that observed in advanced cancer patients receiving placebo [30, 31]. Clinically significant renal deterioration with zoledronic acid is uncommon and is exacerbated by previous exposure to bisphosphonates, underlying malignancy, increased age, dehydration, cumulative doses, and concurrent use of nephrotoxic drugs such as nonsteroidal anti-inflammatory agents and cisplatin [32]. Nevertheless, regular monitoring of renal function prior to administration of intravenous zoledronic acid is strongly recommended in all patients.

Limited comparison studies of bisphosphonates have been performed in an attempt to identify the safest renal profile. A retrospective comparison of risk of renal impairment with ibandronic acid versus zoledronic acid in 333 breast, myeloma, prostate, and non-small cell lung cancer patients found the renal impairment incidence rates (number of events per patient per year of treatment with bisphosphonate) to be significantly higher with zoledronic acid for all tumor sites (0.56 vs 0.21 $p < 0.0001$ when assessed by serum creatinine and 1.92 vs 1.01 $p < 0.0001$ when assessed using glomerular filtration rate (GFR)) for zoledronic acid and ibandronic acid, respectively. Even after adjustment of patient characteristics between both groups, the hazard ratio (HR) for a decline in renal function with zoledronic acid compared to ibandronic acid persisted (HR serum creatinine 1.99, $p = 0.08$; HR GFR 1.94, $p = 0.02$) [33]. Similar results were demonstrated in myeloma patients, while the risk of renal impairment with ibandronic acid increased if patients had received prior zoledronic acid [34]. Comparison of pamidronate 90 mg over 2 h every 3–4 weeks with zoledronic acid 4 mg over 15 min at similar intervals, in breast and myeloma patients, demonstrated no significant difference in renal safety profiles between the two drugs over a period of up to 2 years [35].

In general, provided bisphosphonates are used at the recommended dose and schedule, renal toxicity is unlikely, and serious complications are rare with an incidence of <0.5% [36] (see Table 17.2). The ability to reliably discern which bisphosphonate represents a "safer" option, with lower renal toxicity, would need prospective analysis in appropriately powered comparative trials [19].

17.2.3.4 Gastrointestinal (GI) Toxicity

The most common side effect of oral bisphosphonates is gastrointestinal toxicity, notably to the esophagus or the colon. Recommendations for administration stipulate that oral bisphosphonates should be taken with water, on an empty stomach to prevent food interaction, and the patient remains upright for at least 30–60 min post ingestion.

Placebo-controlled trials of clodronate reported rates of gastrointestinal disorders at 3–10% [37], due mainly to increased diarrhea during the initial treatment phase rather than upper gastrointestinal side effects [38]. Further studies reported clodronate associated diarrhea at 19.9% vs 10% placebo, with only mild upper GI toxicity including nausea and difficulty swallowing tablets [39].

Ibandronic acid placebo trials have reported an overall upper GI toxicity rate of 10%, with upper GI symptoms reported as abdominal pain (2.1%), dyspepsia (7%), nausea (3.5%), and esophagitis (2.1%), all of which were twice as likely to occur on ibandronic acid compared to placebo; however, diarrhea occurred at similar frequency to placebo [40]. Coleman et al. reported on 4 oral dosing regimens of ibandronic acid at 5 mg, 10 mg, 20 mg, and 50 mg compared to placebo and found the frequency of GI adverse events occurring in the first month to be 30% with placebo and 33%, 39%, 41%, and 50% at the four increasing dose levels [41].

Gastrointestinal toxicity may result in poor compliance with oral bisphosphonates, and studies in malignancy have suggested that up to one third of patients will not continue or comply with treatment [42]. Thus intravenous preparations may be preferable if oral preparations become intolerable.

An increased risk of esophageal cancer with the use of oral bisphosphonates has been proposed [43, 44]. However, a recent meta-analysis found no increased risk for either esophageal (odds ratio (OR) 1.11; 95% CI, 0.97–1.27) or gastric (OR 0.96; 95% CI, 0.82–1.12) cancers [45].

On the other hand, a consistent reduction in risk of colon cancer has been demonstrated in studies of oral bisphosphonate use. Initially, a case-control study of >900 postmenopausal females diagnosed with colorectal cancer demonstrated that bisphosphonate use for at least a year prior to diagnosis was associated with a significantly reduced relative risk, even when other confounders were taken into account such as diet, body mass index, and use of low-dose aspirin [46]. These findings were supported by a meta-analysis of 6 population-based observational studies reporting 20,001 cases of colorectal cancer in 392,106 patients. In this meta-analysis, a 17% reduction in colorectal cancer incidence was demonstrated (OR 0.83; 95% CI, 0.76–0.90 [47].

17.2.3.5 Cardiovascular

Atrial fibrillation (AF) is the only cardiovascular side effect potentially associated with bisphosphonates. Untreated it can increase risk of stroke, thromboembolism, and cardiac failure. AF has been described in association with the use of pamidronate and zoledronic acid. The first data describing AF as a side effect came from trials in osteoporosis. In an osteoporosis clinical trial of annual zoledronic acid vs placebo in around 3800 postmenopausal women, there was an increased incidence of serious adverse events due to AF with zoledronic acid (1.3% vs 0.6%, $p < 0.001$). The majority of these cases occurred greater than 30 days after a zoledronic acid infusion when serum levels would be undetectable, and thus the mechanism for any relationship was obscure. The increase in AF did not translate to an increase in stroke or thrombosis in the patients [48].

A systematic review and meta-analysis of placebo-controlled trials of bisphosphonates used in osteoporosis, including over 26,000 patients, demonstrated a significant increased risk of AF serious adverse events with BP exposure (odds ratio 1.47; CI 1.01–2.14, *p*-0.04) [49]. In the most recent meta-analysis of 58 randomized trials of bisphosphonate use for >6 months, the possible relationships between bisphosphonate use and cardiovascular events including atrial fibrillation, myocardial infarction, and cardiovascular death were estimated [50]. Bisphosphonate treatment did not have any effects on cardiovascular death (14 trials OR 0.98; 95% CI, 0.84–1.14) or myocardial infarction (10 trials OR 0.96; 95% CI, 0.69–1.34). For atrial fibrillation no relationship overall could be seen (41 trials OR 1.08; 95% CI, 0.92–1.05) although a borderline excess of cases in those treated specifically with zoledronic acid was identified (26 trials OR 1.24 95% CI, 0.96–1.61). Any possible association would therefore appear to be very weak and probably not clinically relevant.

The extrapolation of these data to oncology patients is difficult, but none of the studies to date have demonstrated an increased risk of AF. A recent large adjuvant breast cancer trial of zoledronic acid did not demonstrate any excess cardiac toxicity

in those receiving zoledronic acid compared to standard therapy (0.8% vs 0.6%, respectively) [51].

17.2.3.6 Eye

Eye complications include cataract, ocular inflammation, conjunctivitis, uveitis, scleritis, episcleritis, and cranial nerve palsies due to extraocular muscle edema [52]. They were considered rare [21], but recent series suggest they may be more frequent than previously considered. For example, 8/1001 (0.8%) of patients randomized to zoledronic acid 5 mg for the treatment of osteopenia (none in the placebo arm) had acute anterior uveitis confirmed by an ophthalmologist within 7 days of treatment [53]. Ocular toxicities have also been reported with the non-aminobisphosphonate, clodronate [54], and in post-marketing experience with ibandronic acid.

The onset of ocular inflammation appears to start soon after administration of a bisphosphonate, and the mechanism of action has been proposed to be related to the acute phase response with infiltration of inflammatory cytokines, including interleukin-1 and interleukin-6, into the extraocular muscles [55].

Management involves referral to specialist ophthalmology care. Conjunctivitis is usually self-limiting and often decreases in severity with ongoing bisphosphonate therapy. Several ocular side effects can occur in conjunction and usually resolve over several weeks with termination of therapy [52]. Severe cases of global ocular inflammation, scleritis, or uveitis may need hospitalization and intravenous high-dose steroids [65] although topical corticosteroids are usually sufficient [53]; rechallenge with the causative bisphosphonate is not recommended [21].

17.2.3.7 Central Nervous System

Case reports of seizures associated with zoledronic acid have been published, although in all cases there was an underlying neurological disorder in elderly patients treated for osteoporosis [56]. Many of the reported neurological side effects during bisphosphonate use in malignancy including headache, dizziness, and lethargy are likely to relate to the acute phase response discussed earlier.

17.2.4 Long-Term Adverse Events

17.2.4.1 Osteonecrosis of the Jaw

Osteonecrosis of the jaw (ONJ) was first reported in 2003 in association with pamidronate and zoledronic acid use [57]. Painful bone exposure in the mandible and maxilla was described, commonly occurring after tooth extraction and exacerbated by dental/gingival or jawbone disease, cancer diagnosis, increased age, smoking, diabetes, concurrent chemotherapy or steroids, and potency and duration of bisphosphonate use. The lesions were non-healing and resistant to

antibiotic therapy or debridement. ONJ is a clinical diagnosis and defined as an area of exposed bone in the maxillofacial region that does not heal within 8 weeks after identification in a patient who has not had radiation therapy to the craniofacial region [58].

The causes of ONJ in malignancy are likely to be multifactorial, and although proposed mechanisms include suppressed angiogenesis from aminobisphosphonates and over suppression of bone turnover, the evidence for either of these processes being causative is weak. Immune dysfunction during anticancer therapy can also provide an opportunity for infection and inflammation in the oral cavity, which may exacerbate the potential detrimental effect of bisphosphonates on the jawbone [59].

Because of global market share, most ONJ cases have been associated with the use of pamidronate and/or zoledronic acid. There have been isolated cases with intravenous ibandronic acid, but reports are few and the incidence associated with this agent is not known. ONJ is rare with oral BPs, and the prevalence is reported as less than 0.1% in patients receiving chronic oral BP administration for a range of nonmalignant medical conditions, but whether this reflects the prevalence in malignancy is not known [60]. A recently presented large randomized trial of adjuvant bisphosphonates in early breast cancer patients compared three bisphosphonate treatment strategies. In this trial the rates of ONJ, with a median follow-up of 5.4 years and a 3-year treatment duration, were 27/2094 (1.3%), 7/2151 (0.3%), and 11/1507 (0.7%) for intravenous zoledronic acid, daily oral clodronate, and daily oral ibandronate, respectively [61].

The incidence with monthly intravenous bisphosphonates has been reported from retrospective trials as approximately 5% in patients with metastatic bone disease; however, prospective randomized trials of zoledronic acid vs denosumab indicate the incidence is probably lower at approximately 1.5–3% over 2–3 years of use [62, 63]. The incidence is less when administration is less frequent as used to prevent cancer treatment induced bone loss. Data from a large prospective randomized trial of zoledronic acid in early breast cancer with a median follow-up of approximately 7 years reported an ONJ incidence of 2.1% (95% CI, 0.9–3.3%) [64]. Despite the potential risk for developing ONJ during treatment with an intravenous bisphosphonate, the benefits of bisphosphonates in metastatic malignancy far outweigh this small risk.

Treatment of ONJ is difficult despite local debridement, antibiotics, and oxygen therapy. Thus, the management focus should be on prevention by increasing awareness among oncologists, dentists, and maxillofacial surgeons. Good dental hygiene and avoidance of dental procedures during therapy significantly reduce the risk of ONJ with zoledronic acid [65, 66].

17.2.4.2 Atypical Femoral Fractures

Although bisphosphonates significantly reduce the risk of osteoporotic fragility fractures and have become the cornerstone of osteoporosis treatment, concerns have emerged over the past decade about the association of anti-resorptive

therapy with spontaneous non-vertebral fractures, notably in the femur and known as atypical femoral fractures (AFF) [67]. AFF are characteristically transverse or slightly oblique in nature and occur in the lateral cortex, or tension side, of the subtrochanteric region of the femur where diffuse cortical thickening and fracture can be observed on radiographs. They can be bilateral. Although rare, the risk of AFF has led to restrictions on duration of bisphosphonate use in the treatment of osteoporosis [68]. Unsurprisingly, in view of the increasing long-term use and intensive schedules of treatment used in advanced cancer settings, reports have also emerged in recent years of AFF in cancer patients treated with bisphosphonates. A recent review of 10,587 cancer patients, treated at the MD Anderson Hospital between 2004 and 2013, identified 23 cases. The risk of AFF however was very low at only 0.05 per 100,000 person-years. It also appeared around five times more frequent with alendronate use for treatment induced bone loss than with the other bisphosphonates used for metastatic bone disease [69].

The very small risk of a patient developing an AFF should not restrict use in cancer patients, but clinicians should be aware of the condition and investigate unexplained thigh pain with appropriate imaging and refer for orthopedic assessment.

17.2.5 Conclusions

The use of bisphosphonates in malignancy has been supported by clear evidence from clinical trials of a reduction in skeletal-related events from bone metastases arising from numerous tumor sites including breast, prostate, myeloma, lung, and other solid tumors. Bisphosphonates have also demonstrated efficacy in reducing bone loss associated with adjuvant therapy [19] and have a role in prevention of metastasis from breast cancer [2].

The benefits and risks of bisphosphonate use in both the palliative and adjuvant setting must be carefully considered to ensure the former offsets the latter. Although there can be occasional serious toxicities with bisphosphonates (see Table 17.3), the majority of these can be avoided with increased awareness of potential side effects, appropriate monitoring, and strict adherence to recommended administration guidelines and dosage.

Although renal impairment and ONJ are two potentially serious side effects, they only occasionally lead to a need for discontinuation of the bisphosphonate. Alteration of the infusion time and/or dose with appropriate dental hygiene and management should ensure these are mild, self-limiting side effects. To put the risk benefit into context, the reduction in skeletal complications with zoledronic acid exceeds the risk of ONJ by a factor of >10 [70]. Bisphosphonates have established themselves as an integral part of the treatment of cancer-related bone disease, have a favorable safety profile, and contribute to an enhanced quality of life for many cancer patients.

Table 17.3 Summary of side effects of bisphosphonates and denosumab

Frequency	Oral bisphosphonates	Intravenous bisphosphonates	Denosumab
Common ≥1/100 <1/10	• Asymptomatic hypocalcemia • ↑AST/ALT (within normal range) • Diarrhea • Abdominal pain • Nausea/dyspepsia • Vomiting • Constipation • Headache • Musculoskeletal pain	• Symptomatic hypocalcemia • Hypophosphatemia • Hypomagnesemia • Parathyroid disorder • ↑GGT • ↑Creatinine • Diarrhea • Abdominal pain • Nausea/dyspepsia • Vomiting • Constipation • Pharyngitis • Influenza-like illness • Headache • Bone/joint pain • Cataract/ conjunctivitis • Bundle branch block	• Urinary tract infection • Upper respiratory tract infection • Sciatica • Cataracts • Constipation • Rash • Pain in extremities
Uncommon ≥1/1000 <1/100	• Iritis • Gastritis • Esophagitis • Dysphagia • Duodenitis • Esophageal ulcer	• Osteonecrosis of the jaw[a] • Uveitis • Gastritis • Gastroenteritis • Mouth ulceration • Dysphagia • Cholelithiasis • Myalgia • Anemia/blood dyscrasia • Migraine/neuralgia • Deafness • Myocardial ischemia • Atrial fibrillation • Pulmonary edema • Rash/pruritus • Hair loss • Urine retention/ ARF	• Osteonecrosis of the jaw[a] • Diverticulitis • Cellulitis • Ear infection • Eczema

(continued)

Table 17.3 (continued)

Rare ≥1/10000 <1/1000	• Symptomatic hypocalcemia • ↑PTH • ↑Alk phos • ↑AST/ALT (>2× normal range) • Mild skin hypersensitivity, i.e., pruritus, urticaria • Bronchospasm • Glossitis • Esophageal stricture • Osteonecrosis of the jaw	• Ocular inflammation • Focal segmental glomerulosclerosis • Nephrotic syndrome	• Hypocalcemia (<1.88 mmol/L)
Very rare <1/10000		• Anaphylaxis • Bronchospasm • ONJ • Infection • Leukopenia • Scleritis • Episcleritis • Xanthopsia • Hyperkalemia • Hypernatremia	
Frequency unknown	• Uveitis • Severe bone, joint, and/or muscle pain • Severe hypersensitivity reaction including angioedema, bullous reaction, Stevens-Johnson, toxic epidermal necrolysis, anaphylaxis • Hair loss • Impaired renal function		

Table adapted from Medicines Compendium
[a]Estimated rates for osteonecrosis of the jaw relate to annual risk

17.3 Denosumab

17.3.1 Clinical Indication and Pharmacology

Denosumab is a fully human IgG2 monoclonal antibody that targets receptor activator of nuclear factor-kB ligand (RANKL). RANKL controls the differentiation and activation of osteoclasts [71] by binding to RANK receptors on osteoclasts and its precursors [72]. RANKL-mediated bone resorption is increased in osteoporosis and malignant bone disease due to breast and prostate cancer [73]. Denosumab inhibits RANK ligand-receptor interaction, and this leads to diminished osteoclast activity and survival. As a consequence bone resorption is reduced and bone mineral density (BMD) is enhanced. This effect has been observed in trabecular as well as cortical bones of patients [74]. In addition, there is evidence that RANKL may be involved

in facilitating the development of metastasis to bone from breast cancer [75]. Denosumab is administered at a dose of 60 mg SC every 6 months in postmenopausal patients to treat osteoporosis or to cancer patients receiving aromatase inhibitors or androgen deprivation therapy. In patients with metastatic bone disease, a higher dose and frequency of administration, 120 mg SC every 3–4 weeks, is recommended.

Denosumab has been approved by both the Food and Drug Administration in the United States and the European Medicines Evaluation Agency. It is currently licensed as Prolia™ 60 mg every 6 months to improve bone mass and reduce fracture in osteoporotic postmenopausal females [76]. In the cancer setting, denosumab is approved to reduce treatment-induced bone loss and fracture in nonmetastatic prostate cancer patients having hormone ablation therapy [77] as well as adjuvant breast cancer patients on aromatase inhibitors [78]. Denosumab 120 mg every 4 weeks (Xgeva™) has been shown to be more effective than zoledronic acid for prevention of skeletal morbidity in patients with bone metastases from breast cancer, prostate cancer, and other solid tumors [62, 63, 79]. Trials are currently underway to establish the role of denosumab in preventing cancer recurrence in the adjuvant setting in high-risk breast cancer patients undergoing chemotherapy (NCT01077154) as well as the benefit of treatment in bisphosphonate refractory hypercalcemia (NCT0896454).

In contrast to intravenous bisphosphonates, there are no requirements to reduce the dose of denosumab in patients with renal impairment. The safety of denosumab has not been studied in patients with hepatic impairment, but as monoclonal antibodies are thought to be eliminated by being broken down to peptides and amino acids by an "immunoglobulin clearance" pathway within the reticuloendothelial system and not excreted by the liver, specific dosing recommendations do not appear to be required. Importantly, significant levels of neutralizing antibodies against denosumab have not been demonstrated in clinical trials [62, 63, 74]. There is no experience in drug overdose. The highest dose used in a phase II trial of 180 mg 4 weekly over 21 weeks was well tolerated by breast cancer patients with bone metastases, although hypocalcemia was more common at this dose than the approved 120 mg dose [80].

17.3.2 Animal Toxicology and Teratogenicity

RANK/RANKL "knockout" mice demonstrated reduced lymph node formation and partial inhibition of early T and B lymphocyte development as well as reduced bone growth and lack of tooth eruption [81]. Inhibition of mammary gland formation has been observed in vitro [82]. In cynomolgus monkeys, denosumab did not appear to elicit maternal toxicity, fetal harm, or teratogenicity and did not affect lactation or fetal growth although an excess of stillbirths and postnatal mortality and temporary decreases in weight gain and growth/development were seen [83].

No data exist for humans on the effect of denosumab on fertility or the developing fetus, and therefore its usage is not recommended during pregnancy or in

subjects intending to conceive. In addition, it is unknown whether denosumab is excreted in breast milk, and denosumab is not recommended if there are plans to breast feed. Denosumab is being assessed in children with a range of skeletal conditions including osteogenesis imperfecta and giant cell tumors of bone but is currently not recommended for use in the pediatric population as the long-term safety and efficacy in children remains to be established and effects on developing bone may be detrimental.

17.3.3 Systemic Acute Side Effects

17.3.3.1 Metabolic

Hypocalcemia is the most common metabolic side effect. However in clinical trials where patients also received calcium and vitamin D supplements, clinical manifestations were uncommon, even with prolonged monthly treatment. In 3933 postmenopausal patients treated with denosumab 60 mg 6 monthly over 3 years plus calcium and vitamin D supplements, there were no reported cases of hypocalcemia (adjusted calcium <2 mmol/L) [84]. In trials of patients with bony metastases from solid tumors treated with denosumab 120 mg 3–4 weekly, the overall incidences of hypocalcemia were 10.8% and 13% with grade 3 or 4 hypocalcemia (<1.75 mmol/L) in 2.3% and 5%, respectively [85]. Most events were asymptomatic, occurred once, and only infrequently required intravenous replacement. None were fatal. In one study, 5.7% and 2.7% of patients required intravenous calcium during treatment with denosumab and zoledronic acid, respectively [63]. Phosphate levels can also be seen to transiently drop as bone turnover is reduced, although none of the large clinical trials have reported this specifically as an adverse metabolic effect.

There is an increased risk of hypocalcemia in patients with a history indicative of abnormal calcium metabolism such as previous hypoparathyroidism, thyroid surgery, or severe renal impairment. A recent study has suggested that patients with a high serum alkaline phosphatase level predict for denosumab-induced hypocalcemia [86]. Furthermore, patients with a creatinine clearance of <30mls/min or a patient on renal dialysis is at higher risk and must have calcium levels monitored closely. Denosumab is contraindicated in patients with hypocalcemia, but once corrected, treatment may be initiated or resumed. The manufacturer recommends that all patients should be well supplemented with calcium and vitamin D.

17.3.3.2 Musculoskeletal

Musculoskeletal events were rarely reported in patients treated with 60 mg denosumab 6 monthly, except in adjuvant breast cancer patients taking aromatase inhibitors [78]. Most cases were attributed to the aromatase inhibitor and only a few attributed to the study drug by the investigator. Furthermore, no significant difference in incidence or severity was found compared to placebo [78]. In fact, back pain and arthralgia were significantly more common in patients with bone metastases from breast cancer treated with zoledronic acid compared to high-dose denosumab [62].

17.3.3.3 Skin

Dermatological side effects such as rash, eczema, and injection site reaction have been reported rarely. Only for eczema has a significant difference been found compared to placebo in the incidence rates (3% denosumab vs 1.7% placebo ($p < 0.001$) [76]. However, an excess frequency of eczema has not been reported in other trials.

17.3.3.4 Gastrointestinal

Constipation in patients with bone metastases from solid tumors has been reported in the three bone metastasis trials with incidences of 17.3%, 24%, and 25% [62, 63, 79]. However, constipation was more commonly noted in patients on zoledronic acid in each trial. At lower doses of denosumab, constipation has not been reported as an adverse effect.

17.3.3.5 Ophthalmic

In prostate cancer patients receiving androgen deprivation therapy and denosumab 60 mg, 6 monthly, rates of cataracts were 4.7% compared to 1.2% for placebo [77]. Although none of these cases were considered related to denosumab, a prospective evaluation is underway to assess the risk prospectively for cataracts associated with denosumab use (NCT00925600).

17.3.3.6 Infections and Immune Function

In patients having low-dose denosumab as part of the FREEDOM trial [76], the rate of serious adverse infection was 4.1% compared to placebo 3.4% ($P = 0.14$). There was an increased incidence of cellulitis with denosumab, but overall rates remained very low (0.3% denosumab vs <0.1% placebo $P = 0.002$). In the bone metastasis trials, infections were more common due to the underlying malignancy and concomitant treatments, but no significant excess seen with denosumab. Initial concerns of an increased risk of infection with denosumab have not been supported by the many large randomized trials.

In terms of new primary cancers, cancer recurrence or disease progression, no significant differences between denosumab and either placebo or zoledronic acid across different patient groups and trials have been reported.

17.3.4 Late Adverse Events

17.3.4.1 Osteonecrosis of the Jaw

ONJ has been defined earlier in the chapter. It is very rare in patients treated with denosumab 60 mg 6 monthly [78], and as with bisphosphonates the frequency of ONJ appears to be related to the dose, frequency, and duration of action. The incidence in advanced cancer patients treated with 120 mg 4 weekly remains low and similar to that associated with the use of zoledronic acid. In 2046 patients with bone metastases from breast cancer, the incidence of ONJ was 2.0% with denosumab compared to 1.4% with zoledronic acid, $P = 0.39$ [62]. In a trial of 1904 patients

with bone metastases from prostate cancer, the incidence of ONJ was 2.0% with denosumab compared to 1.0% with zoledronic acid, $P = 0.09$ [79]. A similar incidence was also seen in patients with bone metastases from other solid organs (excluding breast and prostate) or myeloma. Here, the incidence of ONJ was 1.3% with denosumab compared to 1.1% with zoledronic acid ($P = 1.0$) [63]. Risk factors for ONJ in these three studies included poor dental hygiene, concurrent chemotherapy, comorbidities, dental extraction, and previous treatment with bisphosphonates [58]. Most cases could be managed with oral rinses and antibiotics, but occasionally surgical debridement or bone resection was necessary. Approximately 40% of the cases resolved. As with the use of bisphosphonates, regular dental examinations, patient education, and avoidance of invasive dental procedures while on treatment are vital.

The effects of long-term bone suppression with denosumab are still being investigated. Iliac crest biopsies from postmenopausal females treated with denosumab 60 mg 6 monthly for 2 years showed normal bone architecture and no evidence of bone mineralization defects, woven bone, or marrow fibrosis [84]. AFF have been reported with denosumab [87], and concerns persist regarding the increased risk of AFF and delayed fracture healing. Additionally, an excess of rebound vertebral fractures has been reported in patients discontinuing denosumab for treatment of osteoporosis [88], reflecting the short duration of action of the antibody and overcompensation in previously suppressed bone turnover that occurs on treatment withdrawal.

Conclusions

Overall, denosumab is very well tolerated. There is a higher incidence of hypocalcemia with denosumab compared to zoledronic acid. The incidence of ONJ is similar to intravenous zoledronic acid. Hypocalcemia is manageable with adequate calcium and vitamin D supplementation. Denosumab is safe in patients with renal impairment and no dose modification is required. The long-term effects of bone suppression are unknown, and this is of particular relevance in the adjuvant setting. Ease of administration, low toxicity profile, and continued use in patients with worsening renal function make denosumab an attractive therapeutic agent.

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State of the Art of Antiemetic Therapy

18

Sonia Fatigoni and Fausto Roila

Abstract

Despite relevant progress achieved in the last 30 years for the prevention of chemotherapy-induced emesis, nausea and vomiting continue to be among the most distressing adverse events induced by chemotherapy. Emesis is a complex phenomenon, and the precise mechanism by which chemotherapy induces nausea and vomiting is not well known. Many neurotransmitters are involved, and several antiemetic drugs are available. Complete control of vomiting could be achieved in about 70–90% of patients with a better combination of antiemetic drugs.

Recently, international guidelines to prevent chemotherapy-induced nausea and vomiting have been updated, and it is very important to know these recommendations and to use them correctly in our clinical practice. However, several aspects of antiemetic therapy will be clarified in the coming years: the improvement of nausea control, the prophylaxis of emesis induced by oral therapies, and the prevention of emesis induced by chemoradiation therapy.

Keywords

Antiemetics · Chemotherapy · Nausea · Vomiting · Side effects · Chemoreceptor trigger zone (CTZ)

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M. A. Dicato, E. Van Cutsem (eds.), *Side Effects of Medical Cancer Therapy*,
https://doi.org/10.1007/978-3-319-70253-7_18

18.1 Introduction

Significant progress has been achieved in recent years in the prevention of chemotherapy-induced nausea and vomiting. Nevertheless, vomiting and especially nausea continue to be the most important chemotherapy-induced side effects, with significant consequences for patients' quality of life and patients' adherence to chemotherapy.

For these reasons, it is very important in clinical practice to know the different risks of emesis induced by different chemotherapeutic agents, the antiemetic drugs available, and the international antiemetic guidelines.

In the 1990s, several professional organizations published recommendations for antiemetic treatment in patients submitted to chemotherapy and radiotherapy. In the following years, these recommendations were updated, and the last update was published in 2016 [1] by the European Society of Medical Oncology (ESMO) and the Multinational Association of Supportive Care in Cancer (MASCC); these recommendations are available also on the MASCC website [2]. The majority of suggestions refer only to intravenous agents, because no randomized trial has been carried out in patients receiving oral antineoplastic agents (Table 18.1). The American Society of Clinical Oncology (ASCO) guidelines have also been updated, and these recommendations are similar to the European guidelines [3]. The National

Table 18.1 ESMO and MASCC guidelines for the prevention of chemotherapy-induced emesis

Emetogenic potential	Chemotherapy	Recommendations
High (>90%)	Cisplatin	Day 1: 5-HT3 RA + DEX + NK1 RA
		Days 2–3: DEX (or if aprepitant 125 mg on day 1, mcp + dex or apr + dex)
		Day 4: DEX
	AC	Day 1: 5-HT3 RA + DEX + NK1 RA
		Days 2–3: none (or if aprepitant 125 mg on day 1, dex or aprepitant)
Moderate (30–90%)	Carboplatin-based chemotherapy	Day 1: 5-HT3 RA + DEX + NK1 RA
		Days 2–3: none (or if aprepitant 125 mg on day 1, aprepitant)
	Others (see Table 18.2)	Day 1: 5-HT3 RA + DEX
		Days 2–3: no routine prophylaxis (for oxaliplatin or anthracycline or cyclophosphamide, dex can be considered)
Low (10–30%)	See Table 18.2	Day 1: 5-HT3 RA or DEX or dopamine RA
		Days 2–3: no routine prophylaxis
Minimal (<10%)	See Table 18.2	Day 1: no routine prophylaxis
		Days 2–3: no routine prophylaxis

Dex dexamethasone, *Mcp* metoclopramide, *AC* anthracycline, and cyclophosphamide combination

Comprehensive Cancer Network (NCCN) antiemetic guidelines have been updated as well, but it is important to remember that these recommendations, as opposed to the ESMO-MASCC and ASCO recommendations, are opinion-based rather than evidence-based [4].

18.2 Definition and Classification

Nausea is the perception that emesis may occur; it can be evaluated only by the patient. The incidence of nausea correlates with the incidence of vomiting, but nausea generally occurs more frequently than vomiting. Vomiting is forcing the stomach contents up through the esophagus and out of the mouth; it may occur with or without nausea. Chemotherapy-induced nausea and vomiting should be classified as acute, delayed, and anticipatory arbitrarily, based on the time of onset: acute nausea and vomiting occur within the first 24 h after chemotherapy; delayed nausea and vomiting occur 24 h after chemotherapy; anticipatory nausea and vomiting occur before chemotherapy, usually in patients with acute and/or delayed nausea and vomiting experiences in the previous courses of chemotherapy. When the patient returns to receive the following cycle of chemotherapy, emesis may be induced by the smells, sights, and sounds of the treatment room.

Several factors may influence the incidence and severity of chemotherapy-induced emesis.

Some are patient-related: gender, age (females and young patients more frequently have nausea and vomiting), history of alcohol intake, history of emesis during pregnancy or due to motion sickness and anxiety. Other factors are therapy-related: chemotherapy type and dose, infusion rate, and route of administration. However, the most important factor is the presence or absence of acute nausea and vomiting and emesis in previous courses of chemotherapy.

The emetogenic potential of antineoplastic agents should be classified as high (>90% incidence), moderate (30–90%), low (10–30%), and minimal (<10%). However, every classification is arbitrary, because many characteristics of emetogenic potential (frequency, intensity, duration, latency) are not well known for many chemotherapeutic agents, especially oral antineoplastic agents. Recently, the classification of antineoplastic agents has also been updated (Table 18.2).

18.3 Pathogenesis of Chemotherapy-Induced Emesis

Emesis is a complex side effect, and the precise mechanisms by which chemotherapy induces nausea and vomiting are not well known. There are probably two principal pathways, central and peripheral [5], and some mechanisms of activation are described in the following sections.

Table 18.2 Emetogenic potential of intravenous and oral antineoplastic agents[a]

	High (>90%)	Moderate (30–90%)	Low (10–30%)	Minimal (<10%)
IV chemotherapy	Anthracycline/ cyclophosphamide combination, carmustine, cisplatin, cyclophosphamide ≥1500 mg/m^2, dacarbazine, mechlorethamine, streptozocin	Alemtuzumab, azacitidine, bendamustine, carboplatin, clofarabine, cyclophosphamide <1500 mg/m^2, cytarabine >1000 mg/m^2, daunorubicin, doxorubicin, epirubicin, idarubicin, ifosfamide, irinotecan, oxaliplatin, romidepsin, temozolomide, thiotepa, trabectedin	Aflibercept, belinostat, blinatumomab, bortezomib, brentuximab, cabazitaxel, carfilzomib, catumaxomab, cetuximab, cytarabine ≤1000 mg/ m^2, docetaxel, eribulin, etoposide, 5-fluorouracil, gemcitabine, ipilimumab, ixabepilone, methotrexate, mitomycin, mitoxantrone, nab-paclitaxel, paclitaxel, panitumumab, pemetrexed, pegylated liposomal doxorubicin, pertuzumab, temsirolimus, topotecan, trastuzumab-emtansine, vinflunine	Bevacizumab, bleomycin, busulfan, 2-chlorodeoxyadenosine, cladribine, fludarabine, nivolumab, ofatumumab, pembrolizumab, pixantrone, pralatrexate, rituximab, trastuzumab, vinblastine, vincristine, vinorelbine
Oral chemotherapy	Hexamethylmelamine, procarbazine	Bosutinib, ceritinib, crizotinib, cyclophosphamide, imatinib, temozolomide, vinorelbine	Afatinib, axatinib, capecitabine, dabrafenib, dasatinib, everolimus, etoposide, fludarabine, ibrutinib, idelalisib, lapatinib, lenalidomide, olaparib, nilotinib, pazopanib, ponatinib, regorafenib, sunitinib, tegafur uracil, thalidomide, vandetanib, vorinostat	Chlorambucil, erlotinib, gefitinib, hydroxyurea, melphalan, methotrexate, L-phenylalanine mustard, pomalidomide, ruxolitinib, sorafenib, 6-thioguanine, vemurafenib, vismodegib

[a]Modified from the MASCC website

18.3.1 Central Pathway

The principal mechanism is the activation of the chemoreceptor trigger zone (CTZ), located in the area postrema of the brain. The CTZ works through the release of various neurotransmitters, including substance P, dopamine, serotonin, histamine, norepinephrine, apomorphine, neurotensin, angiotensin II, gastrin, and vasopressin. These neurotransmitters activate the vomiting center, located in the brain, near the CTZ. The CTZ can receive and transmit information from/to the other central and peripheral sites.

The nucleus of the tractus solitarius, an area of the medulla oblongata, also plays an important role because it probably contains the highest concentration of serotonin type 3 (5-HT3) and neurokinin 1 (NK1) receptors in the brain.

Moreover, there may be a cortical mechanism, with direct or indirect (psychogenic) cerebral activation; for example, patients with previous experience of nausea and vomiting are more likely to have emesis.

18.3.2 Peripheral Pathway

It is activated primarily by the damage of gastrointestinal mucosa with the release of neurotransmitters or by the direct activation of peripheral neurotransmitter receptors. Serotonin plays a central role: it is released by enterochromaffin cells, and it activates the serotonin type 3 (5-HT3) receptors along the vagus nerve in the gastrointestinal tract.

Many chemotherapeutic agents can induce taste and smell alterations, which may lead to nausea and vomiting.

The vestibular system may also be involved in chemotherapy-induced emesis, and patients with a history of motion sickness are more likely to have chemotherapy-induced emesis.

18.4 Antiemetic Drugs

Several antiemetic drugs are available, and the optimal combination can achieve vomiting control in about 80–90% of patients, with minimal side effects. The most important agents are [6, 7]:

1. Corticosteroids (dexamethasone, methylprednisolone). Their antiemetic mechanism is still unclear; they probably work without the blockage of specific neurotransmitters. Their adverse events when used as antiemetic drugs may be limited to insomnia, euphoria, facial flush, increased appetite, and anal pruritus when administered iv rapidly. They can decompensate diabetes or reactivate gastric/duodenal ulcers, but these side effects are unlikely in short-term use, and their use is contraindicated only in cases of diabetic ketoacidosis and active peptic ulcers.

2. 5-HT3 receptor antagonists (5-HT3 RA: granisetron, ondansetron, palonosetron, tropisetron). They block the serotonin type 3 receptors, both central and peripheral (in the small bowel). Palonosetron, the newest of these agents, has a potent and selective 5-HT3 antagonist action with a plasma elimination half-life of about 40 h, longer than that of ondansetron (4–6 h), granisetron (5–8 h), and tropisetron (7 h). Constipation and headaches are drug class adverse effects and appear in about 10% of patients. All 5-HT3 receptor antagonists have similar tolerability.
3. NK1 receptor antagonists (NK1 RA: aprepitant, fosaprepitant, netupitant, rolapitant). The NK1 RA, to be used always in combination with other antiemetics, were initially available as aprepitant tablets to be administered for 3 consecutive days and more recently as an intravenous single dose (fosaprepitant) or oral single dose (rolapitant or netupitant) administered before chemotherapy. This receptor is usually bound by substance P, an 11-amino acid neuropeptide located primarily within the gastrointestinal tract and the central nervous system. It can induce emesis when injected into the ferret by binding to the NK1 receptor. The NK1 RA are able to antagonize this effect of substance P and also the emetic stimulus induced by morphine, chemotherapy, radiation, and anesthesia. They are usually well tolerated.

   A novel long-acting NK1 receptor antagonist, rolapitant, has recently been approved at the dose of 180 mg orally.

   A combination of a novel NK1 RA, netupitant, plus palonosetron (NEPA) has also been approved recently. NEPA is an oral drug containing 300 mg of netupitant and 0.5 mg of palonosetron.

   NK1 RA may present several drug-drug interactions; therefore, it is important to verify this aspect during antiemetic treatment. Aprepitant, fosaprepitant, and netupitant are metabolized by the cytochrome P-450 isoenzyme 3A4 (CYP3A4), the major metabolic pathway for drugs in humans [8]; they decrease, for example, the plasmatic level of oral contraceptives and tolbutamide; they may increase the plasmatic level of benzodiazepines and corticosteroids, which require a dose reduction of around 50%; they can influence the plasmatic level of warfarin and the metabolism of some chemotherapeutic agents (docetaxel, vinorelbine, but generally dose adjustments are not required). Rolapitant is a moderate CYP2D6 inhibitor, and it may increase plasmatic level of dextromethorphan, digoxin, pimozide, and thioridazine (the concomitant use with thioridazine is contraindicated); it may influence also the plasmatic level of some chemotherapeutic agents (methotrexate, topotecan, or irinotecan).
4. Dopamine antagonists (metoclopramide, domperidone, prochlorperazine, haloperidol). They have antiemetic activity by blocking dopamine receptors. Metoclopramide may induce extrapyramidal adverse effects, especially in young patients and especially when used at high dosages.
5. Benzodiazepines (lorazepam, alprazolam). They are useful as combination therapy for their sedative, anxiolytic, and amnesic effects. They may induce somnolence.

6. Olanzapine. This is an antipsychotic drug which blocks several neurotransmitters in the central nervous system, such as dopamine receptors D1, D2, and D3; serotonin receptors 5-HT2a, 5-HT32c, 5-HT3e, and 5-HT6; and α1-adrenergic, muscarinic, and histaminic H1 receptors.

18.5 Nausea and Vomiting Induced by Highly Emetogenic Chemotherapy

18.5.1 Cisplatin: Prevention of Acute Emesis

Before the introduction of aprepitant, a combination of a 5-HT3 receptor antagonist plus dexamethasone was indicated for the prevention of acute nausea and vomiting in cisplatin-treated patients.

Aprepitant showed antiemetic activity in several phase II double-blind studies and in two phase III trials with an identical design. The two phase III studies, published in 2003 [9, 10], compared ondansetron, 32 mg plus dexamethasone, 20 mg on day 1, followed by dexamethasone, 8 mg twice a day on days 2–4, with the combination of ondansetron, 32 mg; dexamethasone, 12 mg; and aprepitant, 125 mg on day 1, followed by dexamethasone, 8 mg daily on days 2–4, and aprepitant, 80 mg on days 2 and 3. In the first study, 530 patients were enrolled and, in the second, 569 patients.

The dexamethasone dose was reduced in the aprepitant arm because aprepitant increases dexamethasone plasma concentrations with an approximately twofold increase in the plasmatic level. Because different dexamethasone doses could change the efficacy of the antiemetic regimen, a 40–50% reduction of the oral dexamethasone dose was made in the aprepitant arm.

The primary endpoint was complete response (no emesis, no use of rescue antiemetics) over the 5-day study period. In both studies complete response was significantly superior with aprepitant (73% vs. 52%, 63% vs. 43%). Complete response on day 1 was also significantly superior with aprepitant (89% vs. 78%, 83% vs. 68%). Complete response from nausea was significantly superior with aprepitant only in the second study. In both studies side effects were mild, with no difference between the two arms.

Another study used a similar design [11], but with prolonged ondansetron in the control arm on days 2–4, with the dose of 8 mg orally twice a day. The aprepitant arm was superior in this case as well.

Concerning the type of 5-HT3 RA, at present all the 5-HT3 RA available are to be considered as having similar efficacy and tolerability in this setting of patients [12]. The single lowest tested fully effective dose, intravenous or oral, should be used before chemotherapy.

Subsequently, fosaprepitant, an intravenous NK1 RA, was approved. When administered intravenously, fosaprepitant is converted within 30 min into aprepitant. A phase III randomized study [13] compared the standard combination of dexamethasone, ondansetron, and aprepitant (125 mg orally, day 1; 80 mg orally,

days 2–3) with dexamethasone, ondansetron, and fosaprepitant (150 mg intravenously, day 1). The study, in which 2322 patients were enrolled, showed the non-inferiority of the fosaprepitant arm.

Recently, two other NK1 RA have been approved, netupitant (in combination with palonosetron, NEPA) and rolapitant.

NEPA has been evaluated in a dose-finding study with 3 doses of netupitant (100 mg, 200 mg, and 300 mg) combined with palonosetron 0.5 mg in 694 patients submitted to cisplatin [14]. Dexamethasone was added to palonosetron alone or to NEPA both on days 1 and 2–5. All doses of netupitant showed superiority compared to palonosetron alone on days 1–5 and 2–5, with a response percentage similar to aprepitant + dexamethasone + ondansetron. The 300 mg dose has been chosen for the phase III trial in patients with breast cancer, based on the superiority of 300 mg even on day 1 and the larger number of patients with no vomiting, no nausea, and with complete protection on days 1–5.

Rolapitant has been evaluated in two randomized trials (HEC-1 and HEC-2) published as a single paper in combination with granisetron and dexamethasone versus granisetron and dexamethasone alone [15]. The two trials enrolled 532 and 555 patients respectively submitted to cisplatin. The primary endpoint was complete protection on days 2–5 (delayed emesis). The dose of rolapitant was 180 mg orally on day 1; the dose of granisetron was 10 μg/kg iv on day 1, and the dose of dexamethasone was 20 mg orally on day 1 and 8 mg twice a day on days 2–4. The rolapitant arm showed a significantly superior complete protection on days 2–5 (HEC-1, 73% versus 58%; HEC-2, 70% versus 62%). The responses were superior only for HEC-1 on day 1 (HEC-1, 84% versus 74%; HEC-2, 83% versus 79%) and on days 1–5 (HEC-1, 70% versus 56%; HEC-2, 68% versus 60%). The patients receiving rolapitant showed also less nausea on days 2–5 and on days 1–5. The side effects were similar.

A phase III randomized trial evaluated olanzapine versus aprepitant in 251 patients submitted to cisplatin or to cyclophosphamide plus doxorubicin [16]. The patients were randomized to receive olanzapine 10 mg orally + palonosetron 0.25 mg iv and dexamethasone 20 mg iv on day 1 and olanzapine 10 mg orally on days 2–4 or aprepitant 125 mg orally + palonosetron 0.25 mg iv and dexamethasone 12 mg iv on day 1 and aprepitant 80 mg orally on day 2–3 and dexamethasone 4 mg twice a day orally on days 2–4. The complete response on day 1 was similar (97% versus 87%), such as on days 2–5 (77% versus 73%). The complete response of the nausea on days 1–5 was superior with olanzapine (69% versus 38%). Unfortunately, many shortcomings compromised the study results: this is not a blind study, the number of patients enrolled was able to demonstrate big differences (≥15% of complete response on days 1–5), the study design was not specified, and finally a non-planned interim analysis was performed.

Recently, two studies (a phase II study and a phase III study) evaluated olanzapine combined with a three-drug combination of a 5-HT3 RA, dexamethasone, and aprepitant in patients submitted to cisplatin or AC chemotherapy [17, 18]. These studies showed high complete response rates and high protection rates against nausea.

Based on these results, a combination of a 5-HT3 RA, dexamethasone, and NK1 RA should be recommended to prevent acute nausea and vomiting induced by highly emetogenic chemotherapy.

18.5.2 Cisplatin: Prevention of Delayed Emesis

The main risk factor for delayed nausea and vomiting is the presence of acute nausea and vomiting, so the incidence of delayed emesis is high in those patients who experienced acute emesis. Therefore, the guidelines recommend that all patients submitted to cisplatin-based chemotherapy receive the adequate prophylaxis for acute and delayed emesis.

Before the introduction of NK1 RA, the recommended therapy was with dexamethasone (8 mg twice a day on days 2–3, and 4 mg twice a day on days 4–5) and oral metoclopramide (0.5 mg/kg four times a day on days 2–5) or a 5-HT3 RA.

In the two previously mentioned phase III trials with aprepitant, complete response on days 2–5 was significantly superior with aprepitant plus dexamethasone than with dexamethasone alone (75% vs. 56% and 68% vs. 47%, respectively).

Unfortunately, in both studies, patients received two different combinations of drugs for acute emesis prevention, and the difference in acute emesis protection may influence the incidence of delayed emesis between the two arms.

Moreover, the combination of aprepitant and dexamethasone has been compared with dexamethasone alone and not with the standard delayed emesis prophylaxis, such as the combination of dexamethasone and metoclopramide.

A randomized, double-blind trial of Italian Group for Antiemetic Research (IGAR) evaluated this topic [19]. The patients (288) submitted for the first time to cisplatin-based chemotherapy receive a combination of aprepitant, dexamethasone, and palonosetron on day 1. They are randomized to receive dexamethasone 8 mg orally twice a day on days 2–4 and metoclopramide 20 mg orally four times a day on days 2–4 versus aprepitant 80 mg on days 2–3 and dexamethasone 8 mg orally on days 2–4. The complete response on day 1 and on days 2–5 was not significantly different. It is necessary to underline an EMA alert which defines 30 mg the maximum daily dose of metoclopramide, because of the risk of extrapyramidal syndromes.

After the approval of the other NK1 RA, the guidelines recommend dexamethasone alone for delayed emesis control. In case of aprepitant used on day 1, aprepitant or metoclopramide and dexamethasone should be used for prevention of delayed emesis.

18.5.3 AC-EC Regimen: Prevention of Acute Emesis

The combination of anthracycline and cyclophosphamide represents a particular situation, with high risk of nausea and vomiting, especially in young women with breast cancer.

A double-blind study [20], randomizing 866 patients receiving anthracycline and cyclophosphamide, evaluated the efficacy of aprepitant combined with a 5-HT3 antagonist and dexamethasone. The patients received on day 1 aprepitant, 125 mg orally, plus dexamethasone, 12 mg intravenously, plus ondansetron, 8 mg before and 8 mg after chemotherapy, or dexamethasone, 20 mg intravenously, plus ondansetron, 8 mg before and 8 mg after chemotherapy. On days 2–3, the patients received aprepitant, 80 mg orally, once a day or ondansetron, 8 mg, twice a day.

The complete response over the 5-day study period was significantly superior with aprepitant (51% vs. 42%); the complete response was also significantly superior with aprepitant on day 1 (76% vs. 69%) and on days 2–5 (55% vs. 49%). Complete response from nausea was not significantly different. In both the studies, side effects were mild, with no difference between the two arms.

Recently NEPA has been evaluated in a randomized clinical trial in 1455 breast cancer women submitted to anthracycline-cyclophosphamide-based chemotherapy for the first time [21]. The study compared NEPA versus palonosetron, both combined with orally dexamethasone at dose of 12 mg and 20 mg, respectively. The primary endpoint was the complete response on days 2–5. NEPA was significantly superior both on days 2–5 (77% versus 70%) and on day 1 (88% versus 85%) and on days 1–5 (74% versus 67%).

Another trial evaluated rolapitant in 1332 patients submitted to moderately emetogenic chemotherapy (80% were female patients, over 50% with breast cancer received anthracycline-cyclophosphamide-based chemotherapy) [22]. Rolapitant was administered on day 1 at the dose of 200 mg orally, dexamethasone at the dose of 20 mg orally on day 1, and granisetron at the dose of 2 mg on days 1–3 orally. The primary endpoint was the complete response on days 2–5. It was significantly superior with rolapitant on days 2–5 (71.3% versus 61.6%) and on days 1–5 (68.6% versus 57.8%). Superior but not statistically significant was the response on day 1 (83.5% versus 80.3%). Nausea and side effect incidence was similar.

Moreover, also in patient submitted to AC regimens, olanzapine way have a role, as mentioned above.

In conclusion, to prevent acute nausea and vomiting in women receiving a combination of anthracycline and cyclophosphamide, a three-drug regimen, including a single dose of 5-HT3 RA, dexamethasone, and a NK1 RA given before chemotherapy, is recommended.

18.5.4 AC-EC Regimen: Prevention of Delayed Emesis

For the women submitted to the combination of anthracycline and cyclophosphamide, receiving aprepitant plus 5-HT3 antagonist plus dexamethasone for the prevention of acute emesis, aprepitant or dexamethasone is recommended to prevent delayed emesis.

Dexamethasone versus aprepitant has been compared in a randomized, double-blind trial of Italian Group for Antiemetic Research. The patients submitted for the first time to anthracycline-cyclophosphamide chemotherapy receive a combination

of aprepitant, dexamethasone, and palonosetron on day 1; they are randomized to receive aprepitant on days 2–3 or dexamethasone on days 2–3 [23]. The results showed similar results of complete protection on day 1 and days 1–5. Similar results were also achieved for secondary endpoints (no vomiting, no significant nausea, complete protection percentage). Concerning the side effects, insomnia and heartburn were more frequent with dexamethasone (2.9% versus 0.4% and 8.1% versus 3.6%, respectively), but with minimal impact in clinical practice.

Two randomized phase III, non-inferiority trials evaluated the possibility of reducing the duration of dexamethasone therapy in delayed emesis, using palonosetron as 5-HT3 antagonist, to minimize the possible side effects related to corticosteroids.

In the first study [24], 300 female chemotherapy-naive patients with breast cancer were enrolled. The patients were submitted to anthracycline-cyclophosphamide chemotherapy, and they received a combination of palonosetron, 0.25 mg intravenously, and dexamethasone, 8 mg, on day 1; then, they were randomized to receive placebo or dexamethasone, 4 mg orally twice a day on days 2–3. During the overall period of study of 5 days, the complete response was similar in both arms: 53.6% versus 53.7%, respectively; similar non-inferiority results were achieved in the acute phase (69.5% vs. 68.5%) and in the delayed phase (62.3% vs. 65.8%).

In the second study [25], 322 patients receiving moderately emetogenic chemotherapy for the first time were enrolled. The chemotherapy included anthracycline-cyclophosphamide combination, oxaliplatin, carboplatin, or irinotecan-based therapy. The patients received palonosetron, 0.25 mg intravenously, and dexamethasone, 8 mg intravenously, on day 1; then, they were randomized to receive no additional therapy or dexamethasone, 8 mg orally, on days 2–3.

During the overall period of study of 5 days, the complete response was similar in both arms: 67.5% versus 71.1%, respectively; similar non-inferiority results were also achieved in the acute phase (88.6% vs. 84.3%) and in the delayed phase (68.7% vs. 77.7%). Therefore, both the studies seem to demonstrate a lack of efficacy against delayed emesis of dexamethasone when used in patients receiving palonosetron. On the other hand, the studies are non-inferiority studies with a sample size calculated considering equivalent of the drug if the complete response was inferior to 15%. Furthermore, a NK1 antagonist was not included in the combination. We think that further larger studies should be conducted to clarify the problem.

18.6 Nausea and Vomiting Induced by Moderately Emetogenic Chemotherapy

18.6.1 Prevention of Acute Emesis

For the prevention of acute emesis induced by moderately emetogenic chemotherapy, a combination of dexamethasone and 5-HT3 RA should be used.

Three studies and a meta-analysis of randomized trials evaluated the efficacy of palonosetron in this situation [26–29].

In the first two trials, two different doses of palonosetron (0.25 and 0.75 mg intravenously) were compared with dolasetron [26] and ondansetron [27], in patients chemotherapy-naïve or pretreated, receiving moderately emetogenic chemotherapy. Palonosetron was superior in both trials. Unfortunately, in these trials the 5-HT3 RA was not combined with dexamethasone, as recommended by guidelines. Moreover, in both studies only 5% of patients received dexamethasone combined with 5-HT3 RA in the acute phase and no one in the delayed phase, and this may be a confounding factor.

In the third trial [28], palonosetron, 0.75 mg intravenously, was compared with granisetron, both combined with dexamethasone in patients receiving high emetogenic cisplatin-based or AC-based chemotherapy. The acute emesis control was similar in both arms, while palonosetron showed superior efficacy for delayed emesis control. In this study, patients with a different emetogenic risk were randomized, and dexamethasone was used at different doses with respect to those recommended by guidelines.

In conclusion, the superiority of palonosetron has not been definitely clarified when different 5-HT3 RA are associated with an NK1 RA and dexamethasone.

Recently aprepitant has been evaluated in 297 patients submitted to carboplatin and paclitaxel for gynecological cancer in a randomized phase III trial [30]. The patients received aprepitant versus placebo, both combined with a 5-HT3 receptor antagonist and dexamethasone. Aprepitant was superior in all the primary endpoints: complete response (61.6% versus 47.3%), no vomiting (78.2% versus 54.8%), and no significant nausea (85.4% versus 74.7%).

Other subgroup analyses of studies evaluating the new NK1 RA suggest a possible utility of the NK1 RA in carboplatin-treated patients.

Based on these trials, NK1 RA, combined with a 5-HT3 RA and dexamethasone, should be used in patients submitted to carboplatin-based chemotherapy.

For other MEC the role of NK1 RA is not yet well defined.

18.6.2 Prevention of Delayed Emesis

The incidence of delayed emesis depends on the incidence of acute emesis: in fact, it is low (12% delayed vomiting and 14% delayed nausea) if the patients did not have acute emesis; instead, it is high (55% delayed vomiting and 75% delayed nausea) if the patients had acute emesis.

The guidelines recommend to consider the prophylaxis with dexamethasone for delayed emesis induced by moderately emetogenic chemotherapy with potential for delayed emesis (oxaliplatin, doxorubicin, cyclophosphamide).

This recommendation has been based especially on a large trial of the Italian Group for Antiemetic Research that demonstrated oral dexamethasone superior with respect to placebo with 10% difference in complete response [31]. The recommended dose is 4 mg orally twice a day on days 2–4.

18.7 Nausea and Vomiting Induced by Low or Minimally Emetogenic Chemotherapy

Only a few trials have been carried out in patients submitted to low and minimal emetogenic chemotherapy, so there is very little evidence. Moreover, the number of agents with low and minimal emetogenic risk was increased with the addition of several target therapies, and there is the possibility of an over- or undertreatment by antiemetics.

Nevertheless, the guidelines recommend that the patients submitted to chemotherapy with low emetogenic risk should receive a single antiemetic agent, such as dexamethasone, or a 5-HT3 RA or a dopamine RA to prevent acute emesis.

The patients submitted to chemotherapy with minimal emetogenic risk should not routinely receive antiemetic prophylaxis before chemotherapy, if they do not have a history of nausea and vomiting.

No antiemetic prophylaxis should be administered for the prevention of delayed emesis induced by chemotherapy with low and minimal emetogenic risk.

18.8 Chemotherapy-Induced Anticipatory Nausea and Vomiting

Anticipatory emesis occurs before chemotherapy, usually in patients who experienced nausea and vomiting in previous chemotherapy courses. Several other factors may be associated with anticipatory nausea and vomiting: the number of chemotherapy cycles, age, sex, and anxiety. In fact, young patients, females, with a history of anxiety have a higher incidence of anticipatory emesis.

The guidelines recommend the best control of acute and delayed emesis as the best way to prevent anticipatory nausea and vomiting. Antiemetic agents usually given in the prevention of acute and delayed nausea and vomiting are often ineffective in treating anticipatory emesis. Behavioral techniques could be effective in reducing anticipatory symptoms, including progressive relaxation technique, desensitization, and hypnosis. Benzodiazepines may help to reduce the incidence of anticipatory emesis, but their efficacy decreases during the treatment.

18.9 Radiotherapy-Induced Nausea and Vomiting

Radiotherapy also is often associated with nausea and vomiting. Incidence and severity of radiotherapy-induced emesis depend on several factors, similar to chemotherapy-induced emesis. Some factors are patient-related (age, gender, state of health, previous history of emesis), and others are treatment-related (irradiated site, single and total dose, fractionation, irradiate volume, radiotherapy techniques). Concurrent or recent chemotherapy is also an important factor. Overall cumulative incidence of emesis is estimated to be around 50–80% of patients undergoing radiotherapy.

Table 18.3 ESMO and MASCC guidelines for prevention of radiotherapy-induced emesis[a]

Emetogenic potential	Radiotherapy	Recommendations
High (>90%)	Total body irradiation	5-HT_3 RA + DEX
Moderate (60–90%)	Upper abdomen, craniospinal	5-HT_3 RA + optional DEX
Low (30–60%)	Cranium, head and neck, thorax region, pelvis	Prophylaxis or rescue with a 5-HT_3 RA
Minimal (<30%)	Extremities, breast	Rescue with a dopamine RA or a 5-HT_3 RA

[a]Modified from the MASCC website

This may be a major problem, considering that fractionated radiotherapy involves a period of 6–8 weeks and prolonged nausea and vomiting may significantly decrease patients' quality of life.

Only a few randomized studies, and often with a small number of patients, evaluated the problem of radiotherapy-induced emesis, so only a little evidence is available. It is very important to investigate the role of individual risk factors, the incidence of delayed nausea and vomiting, the potential role of NK1 receptor antagonists, and the optimal duration of antiemetic prophylaxis [32].

Nevertheless, the guidelines proposed new recommendations, considering four levels of risk (high, moderate, low, and minimal), based on the irradiation area as the most important risk factor (Table 18.3). In the case of chemoradiotherapy, the antiemetic regimen is determined by the chemotherapy antiemetic recommendations of the corresponding risk level, unless the radiotherapy-related risk is higher.

18.10 Special Topics

18.10.1 Nausea and Vomiting Induced by Multiple-Day Cisplatin Therapy

Only a few studies evaluated antiemetic therapies in these patients. About 55–83% of complete protection from vomiting has been achieved with a combination of dexamethasone and 5-HT3 antagonist administered all days of chemotherapy.

The old guidelines recommended a combination of dexamethasone and 5-HT3 antagonist to prevent acute emesis and dexamethasone to prevent delayed emesis, but the optimal dose of dexamethasone and of 5-HT3 antagonist is unknown, as well as the optimal duration of antiemetic therapy [33].

Patients have more severe nausea and vomiting on days 4 and 5, both in studies evaluating dexamethasone 20 mg on each day of cisplatin therapy or only on days 1 and 2, and it is unclear if this could reflect delayed emesis from days 1 and 2. The use of dexamethasone for 5 consecutive days, followed by three additional doses on days 6–8 (for delayed emesis prevention), may be an overtreatment, especially if repeated every 3 weeks for three or four courses, with side effects such as insomnia, agitation, weight gain, epigastric discomfort, and risk of femur osteonecrosis.

The possible role of NK1 RA has been evaluated in some phase II trial and in a small phase III trial.

The phase III trial is a double-blind, crossover study, carried out in 69 patients with germ cell cancer, submitted to 5-day cisplatin chemotherapy [34]. The patients were randomized to receive aprepitant, 125 mg on day 3 and 80 mg on days 4–7, plus dexamethasone, 4 mg orally twice a day on days 6–8, or placebo plus dexamethasone, 8 mg twice a day on days 6–7 and 4 mg twice a day on day 8. A 5-HT3 RA on days 1–5 plus dexamethasone, 20 mg on days 1 and 2, were utilized in both arms. A complete response was achieved in 42% of patients in aprepitant arm versus 13% in the placebo arm.

Based on these data, aprepitant + 5-HT3 RA + dexamethasone are recommended; nevertheless further larger studies are necessary to confirm these interesting results and to clarify the better combination, dose, and schedule of antiemetic drugs in these patients.

18.10.2 Emesis Induced by Multiple-Day Chemotherapy

Recently transdermal granisetron patch has been approved for the prevention of nausea and vomiting in patients who would have difficulty swallowing medicines and receiving moderately and/or highly emetogenic chemotherapy for 3–5 consecutive days. The patch contains 34.3 mg of granisetron and releases 3.1 mg of granisetron per 24 h for up to 7 days. The effectiveness of the transdermal granisetron patch has been evaluated in a randomized, parallel group, double-blind, double-dummy study [35]. The study compared the efficacy, tolerability, and safety of transdermal granisetron patch with 2 mg oral granisetron once daily in 641 patients receiving multi-day chemotherapy. The granisetron patch was applied 24–48 h before the first dose of chemotherapy and kept in place for 7 days. Oral granisetron was administered daily for the duration of the chemotherapy.

The primary endpoint of the trial was complete response from the first administration until 24 h after the start of the last day's administration of chemotherapy and showed the non-inferiority of the granisetron patch with respect to oral granisetron (60% versus 65%). The side effects were similar (constipation 7% versus 3%, respectively, and headache 0.3% versus 2.5%).

18.10.3 Nausea and Vomiting in Children

This aspect of chemotherapeutic treatment for children is often under-evaluated. It has been estimated that about 70% of children receiving chemotherapy experience nausea and vomiting. Published studies present many problems, such as a low number of patients and non-optimal design, so it is impossible to give a specific recommendation for many aspects of antiemetic therapy. Moreover, it is inappropriate to assume that the adult therapy can be directly applied to children, because efficacy and side effects of antiemetics may be different.

Recently two trials have been published evaluating the role of NK1 RA, and the guidelines recommend a combination of aprepitant and a 5-HT3 RA plus dexamethasone to prevent acute nausea and vomiting in children receiving high emetogenic chemotherapy; aprepitant + 5-HT3 RA should be used in children who cannot receive dexamethasone. Some other trials are ongoing. The optimal dose and schedule of antiemetic drugs in children are not yet well known, such as the optimal therapy for delayed emesis or for anticipatory emesis.

18.10.4 High-Dose Chemotherapy

There are very few data on the effective use of antiemetics for patients treated with high-dose chemotherapy with stem cell support. The combination of a 5-HT3 receptor antagonist with dexamethasone represented the old standard of care, with complete protection being reached in a minority of patients. One of the major problems is that in these patients nausea and vomiting depend on several factors, including prophylactic antibiotics, narcotic analgesics, the administration of several highly emetogenic antineoplastic agents over consecutive days and the use of irradiation. All these factors make the research more difficult; nevertheless, randomized trials evaluating new antiemetic drugs are necessary to optimize the prophylaxis.

Recently aprepitant has been evaluated in two randomized clinical trials.

In the first trial, 179 patients submitted to preparative regimens and then to autologous stem cell transplantation [36] were randomized to receive ondansetron and dexamethasone plus or minus aprepitant or placebo daily and for 3 days after completion of chemotherapy. Complete response was 82% versus 66%; no difference in nausea.

The second study evaluated 362 patients submitted to high-dose melphalan and autologous stem cell transplantation [37]. Patients with multiple myeloma were randomly assigned to receive either aprepitant (125 mg orally on day 1 and 80 mg orally on days 2–4), granisetron (2 mg orally on days 1–4), and dexamethasone (4 mg orally on day 1 and 2 mg orally on days 2–3) or matching placebo, granisetron (2 mg orally on days 1–4), and dexamethasone (8 mg orally on day 1 and 4 mg orally on days 2–3). Complete response was better with aprepitant (59% versus 42%), such as the vomiting incidence (22% versus 35%) and the significant nausea (6% versus 12%). Aprepitant has not yet been approved for this indication; nevertheless, its use may be recommended.

18.10.5 Breakthrough Chemotherapy-Induced Emesis and Refractory Emesis

Breakthrough chemotherapy-induced emesis, defined as emesis and/or nausea occurring despite adequate prophylaxis, remains an unsolved problem, such as refractory emesis, defined as emesis in the previously cycle of chemotherapy but without emesis before the subsequent cycle of chemotherapy.

Recently, olanzapine has been evaluated in patients with breakthrough emesis in a study [38]. The study randomized 108 patients to either olanzapine 10 mg orally for 3 days or metoclopramide 10 mg orally 3 times a day for 3 days. No further emesis was 70% with olanzapine versus 31% with metoclopramide, and no nausea was 68% versus 23%; olanzapine induced mild to moderate sedation.

Another phase II study supports these results [39]; therefore these data suggest a possible use of olanzapine for breakthrough emesis.

18.11 Summary

Major improvements have been achieved in the last 20 years in chemotherapy-induced emesis, especially in the control of vomiting. However, chemotherapy-induced nausea is still difficult to control, and it is one of the most important challenges for the following years. Future trials should be oriented to develop new antinausea drugs and to incorporate new agents into current antiemetic regimens.

Despite the increasing use of new antineoplastic agents (e.g., monoclonal antibodies or tyrosine kinase inhibitors) with minimal emetogenic potential and despite several antiemetic agents being available, nausea and vomiting are still disabling side effects. Therefore, the diffusion and the correct utilization of the guidelines are major objectives.

Future improvement in antiemetic therapy will require well-designed clinical trials to define several unresolved questions: the best control of nausea, prophylaxis of delayed emesis induced by multiple days of cisplatin, control of nausea and vomiting induced by oral chemotherapy, chemoradiation therapy-induced emesis, and emesis in children.

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Side Effects of Nociceptive Cancer Pain Treatments in Adults

19

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Abstract

Pain is unfortunately a frequent symptom of cancer, especially in the advanced stages of disease. Its treatment must be integrated into a comprehensive supportive care approach, which itself must be conducted in parallel with specific therapeutic cancer agents, if indicated, and then integrated into the process of palliative care in the advanced phase.

Several classes of pain killers are available:

- Nociceptive pain medications use non-opioid analgesics, weak opioids, and strong opioids, described in the three levels of the WHO ladder.
- "Pure" neuropathic pain is treated by different drug classes, at least in the front line, such as antidepressants, antiepileptics, and some anesthetics such as ketamine. The analgesics in the WHO ladder, including opioids, are generally less effective for this indication, but they, as well as nondrug treatments, will be tried in case of refractory pain.

For the two types of pain, analgesics are often used in combination with co-analgesics (anxiolytics, corticosteroids, anti-osteoclast inhibitors, antispasmodics, etc.).

It is obviously important to know the main side effects of these different drug classes, in order to prevent them, to inform patients of their possible occurrence, and thereby to promote better compliance. The problem of compliance is indeed particularly acute in the area of pain therapy because patients want to use pain as an indicator of a possible disease progression or of an expected response to specific treatments of cancer, and they fear the side effects of analgesics in general and opioids in particular. The main side effects of analgesics are discussed in this chapter.

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M. A. Dicato, E. Van Cutsem (eds.), *Side Effects of Medical Cancer Therapy*,
https://doi.org/10.1007/978-3-319-70253-7_19

Keywords
Cancer · Pain · Side effect · Pain killer · Analgesic

19.1 Introduction

Pain is unfortunately a frequent symptom of cancer, especially in the advanced stages of disease. Its treatment must be integrated into a comprehensive supportive care approach, which itself must be conducted in parallel with specific cancer therapy, if indicated, and then integrated into the process of palliative care in the advanced phase.

At diagnosis and in the early stages of cancer, 30–45% of patients have moderate to severe pain [1, 2].

This percentage increases on average to 75% in advanced stages. Concerning the intensity of pain, 40–50% of patients have moderate or high pain, and 25–30% describe very strong pain [3]. However, in a prospective national multicenter study carried out to estimate the prevalence and incidence of chronic pain with or without neuropathic characteristics in patients with cancer in France, 1805 of 1885 consecutive outpatients participated in the study in 12 oncology units. Patients without pain at visit 1 were included in the incidence study and were seen at 3 and 6 months after visit 1. The overall prevalence of chronic pain was 28.2% (95% CI: 26.3–30.5), ranging from 22.5% to 35.4%, depending on the location of the primary tumor. Neuropathic characteristics were present in 20.9% of these patients, with a prevalence of 2.9% to 9.7%, depending on primary tumor location [4].

Finally, a number of cured patients (it is difficult to estimate the number) present with sequellar pain from cancer and/or treatments used [5, 6].

We traditionally distinguish two main mechanisms of cancer pain, knowing that these two mechanisms are often entangled with advanced disease:

- Nociceptive pain, which represents 70% of the pain [7]
- Neuropathic pain, corresponding to 30–40% of cancer pain [7]

Several classes of drugs are available:

- The treatment of nociceptive pain uses non-opioid analgesics, weak opioids, and strong opioids, which are described in the three levels of the WHO ladder (Fig. 19.1).

The treatment of nociceptive pain uses non-opioid analgesics, weak opioids, and strong opioids, which are described in the three levels of the WHO ladder (Adapted by permission from MacMillan Publishers Ltd. on behalf of Cancer Research UK: British Journal of Cancer, Krakowski et al. [8], Copyright 2003)

- “Pure” neuropathic pain is treated by different drug classes, at least in the front line, such as antidepressants, antiepileptics, and some anesthetics, such as

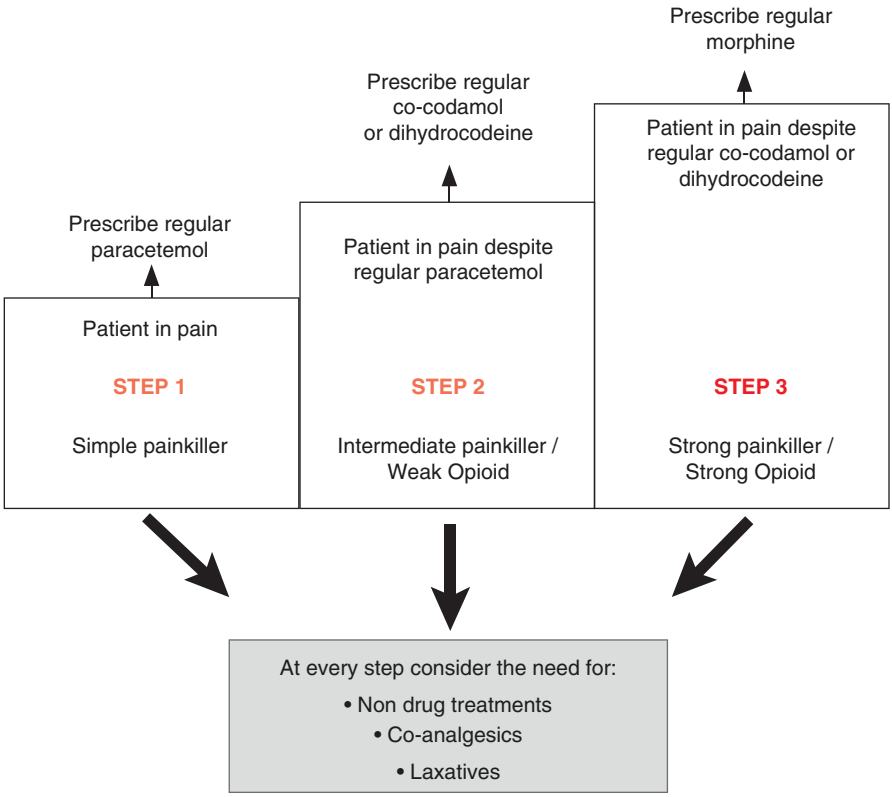

Fig. 19.1 Systemic analgesic pharmacotherapy—the WHO analgesic ladder: Analgesic pharmacotherapy is the mainstay of cancer pain management in parralel with the cancer treatment. Although concurrent use of other interventions is valuable in many patients, and essential in some, analgesic drugs are needed in almost every case. Based on clinical convention, analgesic drugs can be separated into three groups: (1) non-opioid analgesics, (2) opioid analgesics and (3) adjuvant analgesics

ketamine. The analgesics in the WHO ladder, including opioids, are generally less effective in this indication, but they, as well as nondrug treatments, will be tried in case of refractory pain.

In the two types of pain, analgesics are often used in combination with co-analgesics (anxiolytics, corticosteroids, anti-osteoclast, antispasmodic, etc.).

It is obviously important to know the main side effects of these different drug classes, in order to prevent them, to inform patients of their possible occurrence, and thereby to promote better compliance. The problem of compliance is indeed particularly important in pain therapy because patients often use pain as an indicator of disease progression and as a response to specific treatment for cancer, and they fear the side effects of analgesics in general and opioids in particular.

19.2 Side Effects of Non-opioid Analgesics (WHO Level I)

The non-opioid analgesics are used in the treatment of pain of mild intensity (see Fig. 19.1). The main drugs used are paracetamol, anti-inflammatory drugs (NSAIDs at low doses; at high dosages, they are primarily anti-inflammatory), and nefopam.

19.2.1 Paracetamol

Paracetamol is recommended as first choice in mild to moderate pain at a dose of 1000 mg every 4–6 h [9]. Paracetamol can be toxic to the liver when overdosed, justifying precaution for use in cases of liver failure. Liver cell necrosis does occur rarely and with high doses: 8–10 g in a single dose, according to most authors [10]. This product does not alter bleeding time and does not cause thrombocytopenia or leukopenia; it causes neutropenia only in exceptional cases [11]. Finally, in very exceptional circumstances, cases of asthma have been described [12]. It does not alter the renal excretion of water and salts, which facilitates its prescription in patients receiving chemotherapy and renal insufficiency. Liver cell necrosis can occur in three situations: overdose, intoxication in adults with doses beyond 6 g and/or a single dose, and in case of acute alcohol intoxication [9].

Rare cases of hypersensitivity reactions such as anaphylactic shock, angioedema, rash, hives, and skin rash have been reported. These patients should not be treated with this medication and related drugs [10].

Overall, this drug is generally very well tolerated at standard doses [13] and when given up to 6 g/day, if necessary and for a short period, taking into account the benefit/risk ratio. It is appropriate to take particular care in all patients who have hepatic impairment and/or are taking other hepatotoxic drugs.

19.2.2 NSAIDs

The anti-inflammatory drugs include all drugs inhibiting prostaglandin synthesis. These prostaglandins have a purely local, but almost ubiquitous, distribution, acting in many physiological and pathological processes [9].

Prostaglandins are synthesized from arachidonic acid through cyclooxygenase (COX) isoenzymes:

- The COX1 catalyzes the formation of prostaglandins involved in the cytoprotection of gastric mucosa and preservation of renal function and the production of thromboxane A2 (vasoconstrictive prostaglandins and pro-aggregating) by platelets.
- The COX2, essentially an inducible isoenzyme, leads to the release of prostaglandins having a pathological role (fever, pain, inflammation, cell proliferation) but also a beneficial role in various processes (wound healing, kidney function,

ovulation). It governs the synthesis of prostacyclin (vasodilator prostaglandins and anti-aggregating) by endothelial cells.

The decreased synthesis of prostaglandins by NSAIDs is following the more or less selective inhibition of COX isoenzymes. This common mechanism of action of NSAIDs confers their properties and side effects.

COX2 inhibitors (also called coxibs) have not been studied in the context of cancer pain and have no market approval in cancer [5].

Adverse reactions are common to all NSAIDs and can be classified into several groups [14].

19.2.2.1 Gastrointestinal Side Effects

Several different side effects must be distinguished:

- The functional symptoms (dyspepsia, gastric pain, nausea): frequent and rapidly upon discontinuation of product. They are not systematically correlated with the presence of mucosal esophageal or gastroduodenal lesion.
- Peptic ulcers discovered at endoscopy: They are more common with NSAIDs than with coxibs but asymptomatic in half the cases. Small bowel ulcers have been described.
- The symptomatic ulcer, simple or complicated (gastrointestinal bleeding, perforation), of occasionally rapid onset, which occurs in 2–4% per patient year with traditional NSAIDs.

The main predisposing circumstances are a high dosage of NSAIDs, old age, an active or former ulcer, concomitant anticoagulant, a corticosteroid, or other NSAIDs, including aspirin. This risk is about two times lower with coxibs, but this advantage is lost when the patient is given antithrombotic aspirin.

The treatment of gastrointestinal adverse events is by a proton pump inhibitor [5].

The occurrence of gastrointestinal symptoms while the patient is taking NSAIDs should alert one to reconsider the usefulness of NSAID treatment and/or prescription of a proton pump inhibitor and/or the appropriateness of gastroscopy.

Finally, prevention of these injuries must be a priority and can be achieved by a rational prescription of NSAIDs and especially respect for these simple rules:

- Limit the duration of prescriptions.
- Do not associate with other NSAIDs.
- Challenge dangerous associations (antiplatelet agents, anticoagulants).
- Observe the effect, especially in the elderly.

19.2.2.2 Mucocutaneous Reactions

Mucocutaneous reactions consist of pruritus, various eruptions, stomatitis, rhinitis, bronchospasm, and, to a much lesser extent, angioedema or anaphylactic shock. They are the expression of an allergy to the molecule or idiosyncratic state,

including the Widal triad (asthma, nasal polyposis, and aspirin intolerance) and other NSAIDs.

19.2.2.3 Renal Complications

The most common renal complications are early, dose dependent, and consecutive to the inhibition of renal COX:

- Sodium and water retention resulting in lower limb edema, increased blood pressure, or congestive heart failure.
- Acute renal failure, oliguria early on, reversible upon discontinuation of the NSAID. Its occurrence is favored by prior renal hypoperfusion (nephropathy, dehydration, diuretics, etc.) and taking inhibitors of angiotensin converting enzyme or angiotensin II antagonists.
- The concomitant prescription of NSAIDs and other nephrotoxic drugs, including cisplatin, whose elimination is over several weeks, is not to be prescribed owing to risk of renal failure [15].

19.2.2.4 Vascular Complications

All NSAIDs seem likely to favor thrombotic events (myocardial infarction, stroke) through an increase in systolic blood pressure. In combination with anticoagulants, they increase the risk of bleeding.

The blood cytopenias are rare, as well as hepatitis with a clinical expression [15]. Erythema multiforme (Lyell and Stevens-Johnson) is exceptional.

NSAIDs can sometimes cause neurosensory disorders (headache, dizziness, tinnitus, etc.).

19.2.2.5 Drug Interactions with NSAIDs are Numerous

Some associations can be a risky choice and, if indicated, should be discussed with the treatment team—for example, the NSAIDs and low-molecular-weight heparin in a bedridden patient suffering from prolonged difficult-to-control bone pain.

Besides the well-known interaction with cisplatin cited above, one must keep in mind the following interactions:

- Anticoagulants and antiplatelet agents: Concomitant use of NSAIDs increases the risk of bleeding, either because of competition for their protein binding or by interference on hemostasis.
- Methotrexate (MTX) [16]: Concomitant use of NSAIDs leads within hours to days to an increase in the overall toxicity of MTX (association formally not to be recommended).
- Lithium: In principle, one must admit that all NSAIDs, except salicylate, reduce the renal clearance of lithium with a risk of overdose.
- Digoxin: Increased plasma levels owing to decreased renal clearance.
- Antihypertensives and diuretics: The antihypertensive effect of diuretics, beta-blockers, inhibitors of angiotensin converting enzyme, and calcium antagonists can be reduced when taking NSAIDs.

- NSAIDs association: The association of two NSAIDs has no pharmacological advantage.
- Special case: Clinical experience shows that some patients with bone pain and who are taking corticosteroids for another indication may have their pain alleviated by the addition of NSAIDs. However, this association cannot be recommended owing to the lack of studies, and prevention of gastrointestinal side effects is recommended.

Finally, NSAIDs, despite their powerful action, especially in inflammatory pain, are second-line analgesics for cancer pain because of their numerous side effects and risks of drug interactions. Their long-term prescription, that is, over several months or years, can only be considered for uncontrollable chronic pain failing paracetamol, steroids, or opioids alone or in combination. They can be very useful in acute situations or during initial breakthrough pain, for example, for bone pain, when looking for a safer alternative. Whatever the class of NSAID, the dosage, potential side effects, precautions for use, and contraindications are the same.

For any NSAID prescription, it is appropriate to limit the duration of prescription, to not associate two NSAIDs, to avoid dangerous interactions, and to respect the precautions for polymedicated patients, the elderly, and patients with renal failure.

19.2.3 Nefopam

Nefopam has an unclear mechanism of action. It has no opioid property and no anti-inflammatory activity. It is not antipyretic. It inhibits the reuptake of norepinephrine, serotonin, and dopamine [17]. It has anticholinergic effects independent of analgesia. Adverse events [18] reported very frequently are drowsiness, nausea and vomiting, and hyperhidrosis.

Frequently, cases of dizziness, tachycardia, palpitation, dry mouth, and urinary retention have been described.

Rarely, undesirable effects of excitability, irritability, hallucinations, drug dependence, seizures, malaise, and hypersensitivity reactions have been reported.

It should be used with caution in patients with a history of myocardial ischemia and seizures [19]. Its use with tricyclic antidepressants decreases the seizure threshold.

19.3 Side Effects of Weak Opioids (WHO Level II)

Opioids are used in the treatment of pain of moderate intensity. They are represented by codeine, dihydrocodeine, codeine association/paracetamol, tramadol, and tramadol/paracetamol.

19.3.1 Tramadol and Tramadol-Acetaminophen Association

The main side effects attributable to tramadol are nausea and vomiting, drowsiness, headache, euphoria, sweating, dry mouth, and constipation [5, 20].

Nausea is generally dose dependent, and dose reduction during the first days of treatment improves the tolerance. Constipation, euphoria, and respiratory depression are less severe than with level III analgesics [21].

Because of the mechanism of action (preferential mu-opioid receptor agonist activity and central monoaminergic effect by inhibition of neuronal reuptake of serotonin and norepinephrine), tramadol should not be associated with MAO inhibitors. Precaution for use must be taken when prescribed with antidepressants. Indeed, their association can cause a serotonin syndrome, characterized by three groups of symptoms: neuromuscular hyperactivity (tremor, myoclonus, hyperreflexia, pyramidal rigidity), autonomic hyperactivity (hyperthermia, diaphoresis, tachycardia, tachypnea, mydriasis, diarrhea), and altered mental status (agitation, excitement, confusion) [22]. The drugs most frequently responsible for the serotonin syndrome are paroxetine, sertraline, citalopram, fluoxetine, and venlafaxine [23, 24]. Precautions are also taken in case of seizure risk, although the effect of tramadol remains controversial. Particular attention should be paid in patients with a history of head trauma, stroke, or excessive consumption of alcohol [22].

19.3.2 Codeine, Codeine-Paracetamol Combination, and Dihydrocodeine

Codeine and dihydrocodeine generally share the adverse effects of opioids (see below), although they are less intense [25]. They are metabolized by the liver. One must therefore be careful when using them in cases of liver failure.

19.4 Side Effects of Strong Opioids (WHO Level III)

Strong opioids are prescribed in the treatment of pain of moderate to major intensity.

They are classified into several groups, summarized in Table 19.1.

- Strong opioid agonists
- Strong opioid partial agonists or agonist-antagonists
- Strong opioid antagonists

Opioids generally all share the same side effects. The main effects reported in the literature are reported in Table 19.2 [26].

Table 19.1 Classification of strong opioids (WHO level 3)

Strong opioid agonists	Strong opioid partial agonists or agonist-antagonists	Strong opioid antagonists
Morphine	Buprenorphine	Naloxone
Oxycodone	Nalbuphine	
Fentanyl	Pentazocine	
Hydromorphone		
Methadone		
Meperidine or Pethidine		
Sufentanil		

Table 19.2 Common opioid-induced adverse effects

Gastrointestinal	Nausea
	Vomiting
	Constipation
Autonomic	Xerostomia
	Urinary retention
	Postural hypotension
Central nervous system	Drowsiness
	Cognitive impairment
	Hallucinations
	Delirium
	Respiratory depression
	Myoclonus
	Seizure disorders
	Hyperalgesia
Cutaneous	Itching
	Sweating

19.4.1 Nausea and Vomiting

Nausea and vomiting are observed in 15–30% of patients receiving oral morphine as treatment for chronic cancer pain [26].

No study shows an advantage to a specific antiemetic drug. The most frequently used are metoclopramide, haloperidol, phenothiazines, scopolamine patch, and corticosteroids. The use of antagonists of serotonin 5-HT3 (setrons) has not been specifically evaluated in nausea and vomiting induced by opioids in cancer [5].

Uncontrollable nausea and vomiting must induce, if possible, a drug rotation [27–32] or a different route of administration [33, 34]. The subcutaneous route may be less emetogenic [33, 34].

19.4.2 Constipation

Constipation is almost constant and must be systematically prevented with the introduction of opioid therapy [5].

Preventive treatment, whose fundamentals remain empirical, combines lifestyle changes and laxatives.

19.4.3 Dietary Measures

Dietary measures include the following:

- Maintain physical activity whenever possible.
- Increase fluid intake, especially because a dry mouth can occur with morphine.
- Dietary intake balanced with consumption of raw or cooked vegetables, fresh or cooked fruit, dried fruit and nuts (prunes, peanuts, hazelnuts, walnuts, etc.), and preserved fruit. Overconsumption of dietary fiber to fight against constipation related to morphine is not a proven preventive measure. Limitation of foods that slow food transit (rice, chocolate) is empirically recommended.
- Comfortable conditions for a bowel movement (private place, nearness of a commode).

19.4.4 Laxatives

No one laxative has demonstrated its superiority over another [26]. The effectiveness of laxatives is variable from one patient to another. The use of rectal laxatives may be necessary in case of failure of oral laxatives. Protocols are empirical. It is the experience and clinical supervision that will guide the clinician, depending on patient comfort and the choice of products to use.

Rectal laxatives are usually given because of the poor efficacy of oral laxatives. Digital rectal examination helps with the prescription of the following [35, 36]:

- Hard stools: softening laxatives (paraffin, fiber, mucilage, lactulose, polyethylene glycol, etc.).
- Soft stools: laxatives increasing intrarectal pressure (anthracenes, neostigmine, etc.).
- Rectal ampulla empty: discuss a radiograph of the abdomen without preparation, increase the oral laxative treatment (type preparation for colonoscopy), reconsider the oral morphine treatment, and no rectal laxative.

The methylnaltrexone and oxycodone-naloxone combination have demonstrated efficacy [37–39].

Naloxegol, a recent peripheral opioid receptor antagonist laxative, demonstrated no clinical benefit in two randomized, controlled, double-blind studies in the

treatment of opioid-induced constipation in adult patients who have had an inadequate response to laxatives. After 12 weeks of treatment, the effect size in favor of naloxegol 12.5 and 25 mg/day was modest versus placebo, and the efficacy at the daily dose of 12.5 mg/day was poorly established in patients with non-cancer pain. Efficacy and safety have not been assessed in patients with cancer pain [40].

Three recent studies have revealed a trend toward reduction of constipation in patients receiving transdermal fentanyl compared to those treated with oral morphine [41–43].

19.4.5 Sleepiness

Drowsiness is present, according to studies, in 20–60% of patients [26]. It occurs mainly during the adjustment phase of therapy and disappears within a few days. Its reappearance or persistence should suggest a metabolic disorder (renal failure, hypercalcemia, etc.), possibly a potentiation by other sedatives. The benefit of amphetamines and psychostimulants is limited. Some studies indicate that methylphenidate may reduce drowsiness [44–49]. Methylphenidate is not approved in all countries for this indication. Rotation to oral or subcutaneous administration would cause less drowsiness [34]. The severity and prevalence of drowsiness may decrease by changing opioids [28, 30, 31, 50, 51].

19.4.6 Neuropsychiatric Disorders

These disorders can be cognitive (disturbance of consciousness, orientation, memory, attention), behavioral (anxiety, agitation), disorders of perception (hallucinations, dream-like phenomena), and mood disorders (depression, euphoria, exaltation). They are often multifactorial in origin, and an organic cause should always be eliminated.

Reduction of 20–30% of the dose, when possible, can improve these side effects. If this is insufficient, neuroleptics or antidepressants can be used [5, 26].

19.4.7 Myoclonus

These are involuntary muscle movements that are generally dose dependent. Reducing the dosage may allow their control. Drugs such as diazepam, baclofen, midazolam, clonazepam, and valproic acid appear to be able to reduce this side effect [26].

19.4.8 Pruritus

Pruritus is found in 2–10% of cases [26]. The hypothesis of a link between pruritus, release of serotonin, and histamine-induced morphine has been raised [5].

Antihistamines are recommended to treat pruritus [26], and one study [43] mentioned a favorable effect of paroxetine. The use of a setron can be discussed as well as naloxone [5]. Note that fentanyl and hydromorphone would release less histamine than other molecules [26], so changing the molecule could be of interest.

19.4.9 Respiratory Effects

Morphine is a histamine liberator. It thickens the bronchopulmonary secretions and inhibits the cough reflex. Morphine has a respiratory depressant effect, but the pain is a natural agonist of this effect. Therefore, a patient regularly evaluated, suffering from cancer pain and treated with regular escalating doses, has a small risk of respiratory depression [5].

The use of opioids is not indicated in the patient with asthmatic or restrictive respiratory insufficiency. It is advisable to estimate the advantage of the opioid treatment and to be particularly watchful in the therapeutic escalation during an obstructive respiratory failure. A correction of obstruction (mucolytic agents, physiotherapy, etc.), as much as possible, must be implemented. The treatment of respiratory depression involves the prescription of the opioid antagonist naloxone, which is fully effective and rapid. Its dosage should be adjusted considering its half-life (duration of action of intravenous naloxone is 30 min, and 2–3 h for subcutaneous naloxone [5]) and also that of the opioid used.

19.4.10 Other Effects

Dysuria, urinary retention, and sweating have a poorly defined incidence rate. Reducing dosages would improve these symptoms.

For urinary problems, which are associated with an increase in tone of the detrusor muscle and sphincter, a bladder catheter and neostigmine can easily solve the problem [5].

For sweating, NSAIDs and corticosteroids may be tried, even if they do not have market approval for this indication [5].

Tolerance or habituation reflects the need to increase doses of a product to maintain a given effect. Tolerance to the analgesic effect of opioids is low. Most often, the need to increase doses is related to an increase in clinical pain by infra-clinical evolution. However, there is a tolerance benefit to some side effects: drowsiness, respiratory depression, nausea and vomiting, etc.

Chronic use of morphine, like other products, causes physiological changes in connection with its action on specific receptors. Physical dependence is one of those changes. It can lead in the extreme to a syndrome of opioid withdrawal when opioids are stopped abruptly or if an opioid antagonist is prescribed. This phenomenon should not be confused with addiction. The withdrawal syndrome is characterized by anxiety, irritability, chills, piloerection, flushing, sweating, lacrimation, rhinorrhea, yawning, nausea and vomiting, abdominal cramps, diarrhea, joint pain, and mydriasis.

Addiction and physical dependence are problems in patients treated with opioids for cancer pain. Physical dependence requires continuity of the prescription and avoidance of co-prescription of agonist-antagonist opioid receptors [5]. Psychological dependence is, in turn, exceptional [5].

Psychological dependence or addiction is the development of addictive-like behavior, with craving and obsessive attention to obtain the product. Addiction is rare in cancer patients treated with opioids for pain [5, 52].

Some hyperalgesia with morphine may be encountered. These phenomena are currently poorly explained, even though there are interesting hypotheses based on animal experiments [53]. The decrease in dosage or change of opioid sometimes allows a decrease or disappearance of symptoms.

19.5 Side Effects of Other Drugs for the Treatment of Nociceptive Pain

19.5.1 Ketamine

Ketamine is a general anesthetic, not a barbiturate, that is fast acting and has been known for over 40 years. It provides a so-called dissociative anesthesia—that is, loss of consciousness, catalepsy, amnesia, sedation, and analgesia without hypnotic effect. Used since the 1990s at subanesthetic doses for its analgesic activity [54–56], ketamine is commonly used as an intravenous continuous low dose associated with opioid therapy. Its mechanism of action involves various receptors, but especially its effect is a noncompetitive antagonist of *N*-methyl-D-aspartate (NMDA) [55]. Indeed, it is established that the intractable pain, often with a neuropathic component, involves NMDA receptors, located in the central nervous system. Because of repeated stimulation of C fibers and poorly relieved pain, these receptors lead to central sensitization, an increase and an amplification of pain perception. The patient will have an exaggerated pain response during stimulation of C fiber [57, 58].

Adverse effects of ketamine are mainly psychotomimetic [59]. With a subanesthetic dose, patients can express hallucinations or a sense of unreality, sedation, confusion, and salivary or bronchial hypersecretion. These adverse effects can be prevented by adequate prophylaxis based on benzodiazepines, haloperidol, and an anticholinergic and by gradually increasing the dose and the gradual decline of other analgesics [54, 55, 58].

19.5.2 Entonox

Entonox (equimolar mixture of oxygen and nitrous oxide) is presented as a colorless, odorless gas inhaled by mask. The major effects observed with nitrous oxide are a euphoric and anxiolytic effect, an analgesic surface. The use of nitrous oxide at a concentration of 50% does not fit into the context of anesthesia because this concentration is insufficient to induce general anesthesia. With Entonox, the patient

remains alert, there is no respiratory depression or hemodynamic alteration, and laryngeal reflexes are preserved [60].

Side effects are minor and disappear quickly as the administration of gas is stopped [61]. The following effects may occur during treatment and disappear within minutes after cessation of inhalation of the mixture:

- Euphoria and dreams
- Paresthesia
- Sedation
- Dizziness
- Nausea and vomiting
- Changes in sensory perceptions
- Anxiety and agitation

In patients taking drugs that depress the central nervous system, primarily opioids and benzodiazepines, the risk of drowsiness, desaturation, vomiting, and hypotension is increased. Assessment and monitoring by a physician familiar with the use of gas are required.

Neurologic disorders like myeloneuropathies may occur late in patients chronically exposed to high doses. Neurologic toxicity was observed in a case of prolonged inhalation in a context of addiction. After prolonged or repeated exposure, megaloblastic anemia with leukopenia has been reported. It takes more than 6 h of continuous inhalation and over 9 h of intermittent administration to cause bone marrow megaloblastosis without blood changes or clinical signs, and it is reversible upon discontinuation of treatment [62].

Entonox should not be administered in the following situations:

- Patients requiring ventilation with pure oxygen
- Increased intracranial pressure
- Altered consciousness preventing patient cooperation
- Pneumothorax, emphysema
- Abdominal bloating

19.5.3 Ziconotide

Ziconotide is an N-type voltage-dependent calcium channel blocker (NACC) used intrathecally. It is recommended in the treatment of severe chronic pain in patients who require intrathecal analgesia [63]. The main side effects attributed to ziconotide are neuropsychological disorders (dizziness, nystagmus, confusion, gait disturbance, memory impairment, blurred vision, headache, drowsiness) and gastrointestinal disorders such as nausea and vomiting, and asthenia. These side effects are mild to moderate and often disappear over time [63, 64].

These major problems are described in three major studies, summarized in Table 19.3 [65–67].

Table 19.3 Overview of randomized placebo-controlled clinical studies with ziconotide

	Staats [65]	Wallace et al. [66]	Rauck [67]
Titration schedule	Fast[a]	Fast[a]	Slow[b]
Treatment duration (days)	10–11	6–11	21
Population	Patients with pain (VASPI score ≥50 mm) associated with cancer or AIDS	Patients with severe chronic pain (VASPI score ≥50 mm) of nonmalignant cause	Patients with severe chronic pain (VASPI score ≥50 mm) of any cause
Number of patients given Z/P	71/40	169/86	112/108
Pain reported			
Neuropathic (Z/P)	NR	75.7%/76.7%	75.9%/71.3%
Non-neuropathic (Z/P)	NR	13.0%/12.8%	35.7%/32.4%
Mean baseline VASPI score for Z/P group (mm)	74/78	80/77	81/81
Mean decrease in VASPI scores after Z/P	51.4%/18.1% ($p < 0.001$)	31.2%/6.0% ($p < 0.001$)	14.7%/7.2% ($p = 0.036$)
Adverse events			
Nervous system[c]	Dizziness (50.0%), [d]nystagmus (45.8%), somnolence (23.6%), [d]confusion (20.8%), [d]abnormal gait (12.5%)[d]	Dizziness (53.5%), [d]nystagmus (40.0%), [d]abnormal gait (27.1%), [d]somnolence (12.4%), confusion (11.8%), amblyopia (10.6%)[d]	Dizziness (47.3%), [d]somnolence (22.3%), confusion (17.9%), [d]ataxia (16.1%), [d]abnormal gait (15.2%), [d]memory impairment (11.6%)[d]
Digestive system[c]	Nausea (29.2%), [d]vomiting (18.1%), [d]constipation (12.5%)	Nausea (48.8%), [d]constipation (18.2%), vomiting (14.1%)[d]	Nausea (41.1%), diarrhea (18.8%), vomiting (15.2%)
Other systems[c]	Fever (25.0%), [d]postural hypotension (23.6%), [d]urinary retention (18.1%), [d]headache (15.3%)	Pain (16.5%), [d]headache (16.5%), urinary retention (15.3%), [d]postural hypotension (11.8%)	Asthenia (22.3%), headache (15.2%), pain (10.7%)

Adapted from Schmidtko et al. [64], Copyright 2010. With permission from Elsevier

A ziconotide, *P* placebo, *NR* not reported

[a]Fast titration: Initial dosage 9.6 (mu) μg/day, a dose increase 7–14 times per week, maximum dosage per protocol 57.6 μg/day, time to maximum dose 5–6 days

[b]Slow titration: Initial dosage 2.4 μg/day, a dose increase 2–3 times per week, maximum dosage per protocol 21.6 μg/day, time to maximum dose 21 days

[c]Adverse events reported in >10% of patients treated with ziconotide

[d]Occurred with significantly greater frequency with ziconotide than with placebo ($p < 0.05$)

19.6 Summary

Analgesic drugs represent a major focus of supportive therapy. They are applied to fight against some symptoms related to cancer or its treatment; in this chapter, their efficacy against pain was discussed. Treatment of these symptoms must be done with maximum efficiency but also with the least possible side effects in order to avoid a situation in which the remedy is worse than the disease. This implies that professionals are familiar with supportive and palliative as well as specific cancer therapy. To achieve this goal, continuous education in this area must be encouraged. It is recalled here that the handling of opioids, a key factor in cancer pain therapy, follows some simple rules applied to the entire class of drugs. These drugs are extremely safe. In case of overdose, the availability of a good antidote is always effective. Few in our pharmacopeia have such an advantage.

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Totally Implanted Access Ports: Indications and Prevention of Complications

20

Didier S. Kamioner

Abstract

Repeated venipunctures are often aggressive, painful, and sometimes dangerous, especially with the risk of severe extravasation during the administration of anticancer chemotherapy. An implanted central catheter (ICC) can be used for chemotherapy, infusions, transfusions, and blood samples and for the administration of various medications or parenteral nutrition requiring repeated access to the venous system. The installation must be done by a trained operator in surgical aseptic conditions. To prevent complications, training, information, protocols, and evaluation are recommended. Nevertheless, some important complications may occur during installation or use of the device (hematoma, pneumothorax, thrombosis, extravasation, infection, no reflux, etc.).

Keywords

Totally implanted access ports · Venipuncture · Thrombosis · Catheter infection Extravasation · Recall reaction · Huber needle · Venous reflux · Pinch-off syndrome · Costoclavicular clamp

20.1 Introduction

Repeated venipunctures are often aggressive, painful, and sometimes dangerous, especially with the risk of severe extravasation during the administration of anticancer chemotherapy.

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M. A. Dicato, E. Van Cutsem (eds.), *Side Effects of Medical Cancer Therapy*,
https://doi.org/10.1007/978-3-319-70253-7_20

Externalized central catheters are used less frequently and are currently reserved for special situations such as short chemotherapy treatment (less than 3 cycles), terminal palliative care, and intensive care. Peripherally inserted central catheters (PICCs) are frequently used in some countries. This technique, developed in the 1990s in North America, has reduced the indication of conventional central venous insertion; however, it is not currently in use everywhere, due to the lack of familiarity with the equipment. In addition, the incidence rate of infection with PICCs is one to two infections in 1000 catheter days. In comparison, the incidence rate of infection with the ports is 0.1–0.2 infections per 1000 catheter-days. Similarly, the incidence of thrombosis with the port is lower (OR = 0.43, 95; 0.23–0.80). Thus, the implantable central catheter (ICC) is currently the preferred central venous access [1].

The ICC can be used for chemotherapy, infusions, transfusions, and blood samples and for the administration of various medications or parenteral nutrition requiring repeated access to the venous system.

Instructions for the device must be observed rigorously according to the rules defined by tracing items (Code of Public Health). The information delivered to the patient is now largely enshrined in law.

20.2 Installation

The installation [2] must be performed quickly, as soon as the decision of chemotherapy is made, to respect the peripheral venous capital.

It is not appropriate to insert an ICC after the start of chemotherapy because of organizational problems in health-care facilities. This can be done only in cases of true therapeutical emergency, such as enlarged mediastinum in lymphomas or small cell carcinoma. After 1 cycle of chemotherapy, the tumor mass will be reduced and the catheter easily inserted.

The management of antiplatelet agents and anticoagulants is subject to the same rules as any other surgery. Upon installation, the platelet count should be greater than 50,000/mm^3 and the INR (international normalized ratio) lower than 1.5.

When choosing the type of anesthesia to be used—usually a local anesthesia—the preferences of the patient and his or her physical and mental state must be taken into consideration.

The choice of the site must be done in consultation with stakeholders: the patient, the surgeon, the anesthesiologist, and the users (including oncologists, nurses, and therapists). Insertion of an ICC in a pre-irradiated area (apart from contralateral breast cancer after evaluation) or near infected skin metastases is not recommended, and the equipment must be inserted on the opposite side of the tumor (ballistical reasons in case of radiotherapy). The choice of the vein has to be done according to the experience of the operator (preferred superior vena cava: subclavian vein, or internal jugular vein). If implantation in the lower cave system increases the risk of thrombosis and infection, it must still be chosen in certain situations: compression or thrombosis of the superior vena cava, bilateral-jugulo-subclavian thrombosis, extensive skin metastasis, lymphangitis and bilateral cancers.

There are two implementation techniques: the percutaneous and the surgical denudation. The installation must be done in the operating room or in a room reserved specifically for this purpose, by a trained operator in surgical aseptic conditions, preferably under ultrasound guidance, and without antibiotic prophylaxis.

Before the patient is discharged from the operating room, the physician must verify the existence of a blood reflux and flush the ICC with saline serum to ensure the permeability of the system. A chest x-ray should be performed at the end of intervention to check the correct position of the catheter at the junction of the right atrium and superior vena cava and eliminate the risk of pneumothorax. The nurse may use the ICC just after the installation or within days.

The identification card of the equipment must specify the lot number and will then be given to the patient (a copy is kept in the patient's file and another is sent to the pharmacy). A book of his supervision is also provided. An educational approach tailored to the patient or his or her family is undertaken.

20.3 Training, Information, Protocols, and Evaluation

The following procedures are recommended [3–5]:

- The existence of written protocols, shared in a network of care, regularly reviewed, and brought to the attention of caregivers who apply them and whose compliance is assessed
- Staff training in the installation, manipulation, and maintenance of catheters
- Monitoring of infections associated with vascular catheters and their census

For the protection of the personnel, it is imperative to:

- Prevent transmission of infectious agents carried by the blood or the body fluids of the patient.
- Respect general hygiene safety measures, in particular, to make rubbing alcohol first care.
- Provide a secure equipment in order to prevent accidental exposure to blood.

20.3.1 Asepsis

It is recommended that the nursing staff wear sterile gloves during the assembly of infusion lines, during the installation of the Huber needle, and during the bandage change. It is also recommended that the caregivers and the patient wear a mask. If the patient is neutropenic, caregivers must wear a gown over clean business attire and cap.

It is necessary to ensure compliance with the closed system, to limit connections and valve manipulations, and never reconnect a disconnected infusion line.

Twenty-two gauge type II Huber needles (fitted with an extender) with integrated security connector (with a pre-slit septum) should be used preferentially.

The length of the needle must be adapted to the chamber depth and build of the patient. It is recommended to use only syringes with a volume equal to or greater than 10 mL in order to avoid excessive pressure that could damage the ICC. The site of needle insertion should be protected by a sterile bandage that is occlusive, transparent at best, and semipermeable.

The needle is changed every 8 days, maximum, as is the bandage, unless it is contaminated or has been removed. The main line is changed every 96 h. There is no evidence to recommend rinsing with heparin.

Given the risk of infection associated with the handling of a central venous line, maintenance of an implantable venous device table during the intercure or after the treatment is not recommended. A simple clinical surveillance (signs of infection and thrombosis) is necessary. However, a system check is desirable every 3–4 months to find a possible thrombosis of the catheter, a disinsertion of the catheter, a pinch-off syndrome with migration of a piece of the catheter into the heart chambers, or a fibrin muff.

20.3.1.1 Asepsis

- Rinse three times.
- Rotate the needle 360° during flushing.
- Remove the needle while injecting to maintain a positive pressure.
- Immediately remove the needle into a collector, leaving the catheter in a column of saline.
- Place a sterile and occlusive dressing for 1 h.

20.3.1.2 Indicators of Proper Functioning

The absence of one of these four criteria requires immediate verification of the system:

- Presence of venous reflux
- No injection pain
- Good flux of infusion
- Easy injection with a syringe

20.4 Major Complications

Despite compliance with the recommendations regarding the installation and use of ICC, complications may occur.

20.4.1 Mechanical Complications [1, 2, 6]

20.4.1.1 Absence of Reflux

The absence of reflux should always be explored and explained. It can be related to malposition of the needle, a rupture or displacement of the catheter, thrombosis, partial or total occlusion of the catheter, or a sleeve of fibrin. Required additional tests are a chest x-ray; a clouding of the catheter, particularly in the case of an associated painful injection; and a Doppler ultrasound.

20.4.1.2 Pinch-Off Syndrome

The pinch-off must, no matter its rank, lead to a withdrawal and a change of catheter:

- Grade 1: narrowing of the catheter between the clavicle and the first rib with no narrowing of the lumen of the catheter.
- Grade 2: narrowing of the lumen of the catheter.
- Grade 3: fracture with embolization of the catheter. The broken fragment should always be removed using interventional radio-roping techniques.

In case of occlusion of the catheter by a cruoric fibrin deposit, the proper use of fibrinolytic agents according to procedures can "save" the catheter. The best prevention of catheter occlusions is "obsessive" rinsing between two injections and after use.

Complications During Installation or Utilization of ICC [1, 2, 5]

- Hematoma of the operation site
- Pneumothorax
- Hemothorax
- Arterial punctures
- Gaz emboly (exceptional cases 15/7000)
- Pinch-off syndrome or costoclavicular clamp
- Thrombosis
- Infections
- Extravasation

20.4.1.3 Ulceration of the Skin Above the Device [1, 6]

Ulceration of the skin occurs due to the situation of the subcutaneous injection site and may be secondary to a technical error during installation, to a lack of healing after the establishment of the device, to late ulceration of the skin in an emaciated patient, to an unnoticed micro-extravasation, or even to a rejection of the material. In all cases, a surgical approach is necessary to change or replace the device and/or catheter.

20.4.1.4 Extravasation [6]

Extravasation secondary to extravascular injection of cytotoxic molecules is often a serious complication that can cause tissue necrosis and ulceration with severe damages to nerves, joints, and tendons, which sometimes cause major repercussions (chronic pain, muscular dystrophy, loss of function, esthetic repercussions) (Table 20.1).

It is a therapeutic emergency that is undervalued and undertreated. It may delay proper management of the disease by the interruption of chemotherapy and lead to medicolegal procedures. It is essential that the medical and nursing staffs be trained to prevent and manage extravasation.

The rapid establishment of early surgical techniques—drainage washing and suction—is the key factor in preventing the development of irreversible soft tissue damage and/or disabling scarring. Ideally, this procedure should be initiated within 4–6 h following the incident. Without intervention, the lipophilic products

Table 20.1 Extravasation: potential necrosis risk

Drugs	I. Krämer	Cytotoxic handbook	Mader et al.	Quapos 3	CHNIM	CCO	AFSOS St. Paul
Year of publication	2002	2002	2002	2003	2004	2007	2009
Bevacizumab?	–	–	–	–	–	Nonirritant	Nonirritant
Carboplatin	Irritant	Irritant	Nonirritant	Nonirritant	Vesicant	Nonirritant	Irritant
Cisplatin ≤0.4 mg/mL	Irritant	Exfoliant	Irritant	Irritant	Vesicant	Irritant	Irritant
Cisplatin >0.4 mg/mL	–	–	Vesicant	Vesicant	–	–	Vesicant
Cyclophosphamide	Nonirritant	Nonirritant	Nonirritant	Nonirritant	Irritant	Nonirritant	Nonirritant
Docetaxel	Vesicant	Exfoliant	Irritant	Irritant	Irritant	Irritant	Irritant
Doxorubicin	Vesicant	Vesicant	Vesicant	Vesicant	Vesicant	Vesicant	Vesicant
Doxorubicin liposomal	–	Irritant	Irritant	Irritant	–	Irritant	Irritant
Epirubicin	Vesicant	Vesicant	Vesicant	Vesicant	Vesicant	Vesicant	Vesicant
Fluorouracil	Irritant	Inflammatory drug	Nonirritant	Nonirritant	Nonirritant	Nonirritant	Irritant
Méthotrexate	Nonirritant	Inflammatory drug	Nonirritant	Nonirritant	Nonirritant	Irritant-min	Nonirritant
Paclitaxel	Vesicant	Vesicant	Vesicant	Vesicant	Irritant	Irritant	Vesicant
Trastuzumab	–	–	–	–	–	Nonirritant	Nonirritant
Vinorelbine	Vesicant	Vesicant	Vesicant	Vesicant	Vesicant	Vesicant	Vesicant

(e.g., doxorubicin) may persist in the subcutaneous tissue for up to 5 months after the incident.

An emergency kit is essential in each service. The kit should contain a felt pen to mark the area of extravasation, a camera to visualize the area going forward, and the phone number of the surgical team to contact as soon as possible.

In any case, the chemotherapy perfusion should be stopped immediately, but the needle should be left in place.

There is no specific antidote out of dexrazoxane for anthracycline, yet. However, the product has been approved to go to market (AMM) but is not refunded and cannot be replaced or substituted by another dexrazoxane (cardioxane), which is used to prevent cardiac toxicity of anthracyclines.

Reactivation of a preexisting skin lesion (recall reaction) [1, 6] on a previous extravasation site may occur during a subsequent injection through another site. The supposed phenomenon is a synergy between cytotoxic drugs and radiotherapy or between other cytotoxic drugs: anthracycline, cisplatin, mitomycin C, and paclitaxel.

Levels of Risk Associated with Extravasation [6]
Vesicant drugs—responsible for severe necrosis (anthracyclines, vinorelbine, trabectedin, dactinomycin, mitomycin C, vinca alkaloids, etc.):

- Nonvesicant drugs (cyclophosphamide, liposomal doxorubicin, gemcitabine, methotrexate).
- Irritant drugs: responsible for irritations.
- Drugs known as nonirritating do not cause severe reactions.

20.4.2 Infectious Complications [7, 8]

In oncology, the average incidence rate of infection was 0.2/1000 catheter days (0–2.7/1000 days). Infection of the central venous line is a major cause of nosocomial infections and a source of excess morbidity and mortality. The catheter infection requires immediate management and prompt treatment, with or without preservation of the ICC.

Central and peripheral blood cultures with differential time of growth must be performed, but ICC can be retained, unless there are signs of severity (sepsis, local infection, deep thrombophlebitis, or useless equipment). After 48 h, the secondary attitude will depend on the clinical condition, the existence or absence of another focus of infection, the differential time of growth, and the nature of the germ.

About 13% of infections are caused by nosocomial bacteria. These infections prolong hospital stay, delay the administration of specific treatments, increase the problems of antibiotic resistance, and generate incremental hospitalization costs.

20.4.2.1 Thromboembolic Complications [9–11]

The incidence of symptomatic thrombosis of ICC is around 4%. Indications include pain, absence of reflux, arm edema, and so on. It is necessary to perform chest x-rays as well as a systematic echo Doppler to visualize the catheter and the casing when facing any type of dysfunction.

If the primary prevention of catheter thrombosis is not recommended, the curative treatment, however, is compulsory and is based on the prolonged use of low-molecular-weight heparins.

20.4.2.2 Equipment Removal [1, 2]

If the ICC must be performed by a team that specializes in surgical aseptic conditions, it is also the case for its removal. The patient should therefore be informed of the reasons for (end of treatment, occurrence of complications, or poor tolerance) and the consequences of this removal. It seems legitimate to quickly remove a catheter that is no longer used.

20.5 Summary

If the use of totally implanted catheters with subcutaneous chambers has grown considerably, it is important not to trivialize the techniques of both installation and use so as to avoid complications that can sometimes be very severe.

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M. A. Dicato, E. Van Cutsem (eds.), *Side Effects of Medical Cancer Therapy*,
https://doi.org/10.1007/978-3-319-70253-7