Chapter 2
Breast Cancer

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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 hormonal receptors and HER2. Knowledge of treatment-related toxicities as well as patient's comorbidities, preferences, age, and so on is a critical component of an optimal estimation of the benefit versus harm ratio of a specific therapy.

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This chapter reviews the side effects of the four main medical treatment modalities for breast cancer: chemotherapy, endocrine therapy, biologic 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

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 of stage of the disease (early vs. metastatic breast cancer), presence of treatment targets such as hormone receptors and HER2 overexpression or amplification, previous therapies and their effectiveness, extent and location of disease sites (visceral vs. bone and soft tissues), and time course of disease.

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

Once a patient has 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, because the probability of response to subsequent therapies decreases. This is true for sequential endocrine, anti-HER2, or chemotherapy-based approaches.

As a general rule, combination therapies have a tendency to be more highly efficacious in comparison to single-agent therapies, but this comes at a risk of significant 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 agents are reviewed.

Chemotherapy

Classes of Chemotherapy and General Toxicities

Antimicrotubule Agents (Taxanes, Ixabepilone, Eribulin, and Vinca Alkaloids)

Antimicrotubule agents form a large proportion of the chemotherapy agents prescribed in breast cancer patients and either promote microtubule polymerization, stabilizing microtubules and increasing the polymer mass (antimicrotubule stabilizing agents, e.g., taxanes, ixabepilone), or inhibit microtubule polymerization, destabilizing microtubules and decreasing microtubule polymer mass (antimicrotubule destabilizing agents, e.g., eribulin, the vinca alkaloid vinorelbine) [1]. These agents share the toxicities of peripheral neuropathy and myelosuppression.

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

Anthracyclines inhibit topoisomerase II, an enzyme involved in relaxing, 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 [2]. These agents share the toxicities of cardiac injury, myelosuppression, and emesis.

Antimetabolites (5-Fluorouracil, Methotrexate, Capecitabine, Gemcitabine, Pemetrexed)

Antimetabolites have 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 greatest toxicity to cells in S-phase [3], and they have common toxicities that include mucositis, diarrhea, and myelosuppression.

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 [4]. 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 toxicities.

The following section outlines some of the common toxicities associated with breast cancer chemotherapy and their management.

Incidence and Management of Selected Chemotherapy Toxicities

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.

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 another chapter in this book. As far as breast cancer chemotherapy is concerned, particular attention needs to be paid to patients receiving docetaxel, as the rate of febrile neutropenia of 15–20 % is associated with docetaxel at 100 mg/m^2 or anthracyclines plus taxane combinations (rates of febrile neutropenia exceeding 30 %) [31]. For the latter, prophylactic granulocyte colony-stimulating factors (G-CSF) are highly recommended.

The commonly prescribed FEC regimen (5-fluorouracil, epirubicin, cyclophosphamide) induces febrile neutropenic episodes in about 10 % of patients when the epirubicin dose is 100 mg/m^2. Febrile neutropenia is less common with other "popular" breast cancer chemotherapy regimens such as CMF (cyclophosphamide, methotrexate, 5-fluorouracil), weekly paclitaxel, weekly vinorelbine, or capecitabine.

Table 2.1 Side effects of chemotherapy

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
Antimicrotubule: stabilizer	Paclitaxel [5]	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 Arthralgia/myalgia	Nil Nil

Risk factors and recommendation for prevention of SE	Recommendation for management of SE	In the elderly (≥65 years)	Metabolism	Excretion	Cross BBB
Premedication with corticosteroids with or without antihistamines (H1 and H2 antagonists)	Stop infusion	Reduced clearance	Hepatic cytochrome P450 enzymes, primarily CYP2C8/9 and CYP3A4	Biliary	No
	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				
Nil	Symptomatic treatment with paracetamol, NSAIDS, gabapentin, and prednisone (if severe cases)				
	In the curative setting, dose reduction not recommended				

(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
				Peripheral neuropathy (sensory)	Neurological assessments
				Bradycardia and hypotension	Monitor vital signs

Risk factors and recommendation for prevention of SE	Recommendation for management of SE	In the elderly (≥65 years)	Metabolism	Excretion	Cross BBB
Previous neurotoxic chemotherapies, 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				

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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
Antimicro-tubule: stabilizer	Docetaxel [6]	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

Risk factors and recommendation for prevention of SE	Recommendation for management of SE	In the elderly (≥65 years)	Metabolism	Excretion	Cross BBB
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 methyprednisolone [7]	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				

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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
				Rash/pruritus	Nil
				Nail changes	Nil
				Hand-foot syndrome	Nil
				Teary/watery eyes	Nil
				Arthralgia/myalgia	Nil

Risk factors and recommendation for prevention of SE	Recommendation for management of SE	In the elderly (≥65 years)	Metabolism	Excretion	Cross BBB
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 Nailbed 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 [8]				
Nil	Symptomatic treatment with paracetamol, NSAIDS, gabapentin, and prednisone (if severe cases) In the curative setting, dose reduction is not recommended				

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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
Antimicro-tubule: stabilizer	Nanoparticle, albumin-bound paclitaxel; nab-paclitaxel; protein-bound paclitaxel [9]	M IV dose: 300 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	Peripheral neuropathy	Neurological assessments
			Prior therapy should have included an anthracycline unless clinically contraindicated	Ocular/visual disturbance	Nil
				Myelosuppression (neutropenia)	Nil

Risk factors and recommendation for prevention of SE	Recommendation for management of SE	In the elderly (≥65 years)	Metabolism	Excretion	Cross BBB
Influenced by prior and/or concomitant therapy with neurotoxic agents	Grade-3 drug interruption until resolution followed by dose reduction for subsequent cycles	Improved compared to paclitaxel	Liver (primarily via CYP2C8, minor CYP 34A)	Extensive nonrenal	No information available
Dose-dependent	Severe symptoms of sensory neuropathy improve with a median of 22 days after treatment interruption [10]				
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)	Usually rapidly reversible				
Do not give therapy if neutrophil count is <1.5 × 109/L	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				

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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
Antimicro-tubule: stabilizer	Ixabepilone [11]	M	Monotherapy: after failure of taxane, anthracycline, and capecitabine chemotherapy	Peripheral neuropathy	Neurological assessments
		IV dose: 40 mg/m^2 D1 q 3 weekly	Combination therapy with capecitabine: after failure of taxane and anthracycline chemotherapy	Myelosuppression (neutropenia)	Monitor blood count
				Hypersensitivity	Nil

Risk factors and recommendation for prevention of SE	Recommendation for management of SE	In the elderly (≥65 years)	Metabolism	Excretion	Cross BBB
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 12 weeks upon treatment discontinuation	No effects, but limited experience in clinical trials	Liver via CYP3A4	Feces	No information available
Do not give therapy if neutrophil count is <1.5 × 109/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	Stop infusion				
Premedication with IV corticosteroids and antihistamines (H1 and H2 antagonists)	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				

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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
Antimicrotubule: destabilizer	Eribulin [12]	M (Third line and beyond) IV dose: 1.4 mg/m^2 D1,8 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
Antimicrotubule: destabilizer	Vinorelbine [13]	M (First line and beyond) IV dose: mostly used at 20–25 mg/m^2 weekly	NA	Acute dyspnea and severe bronchospasm [14, 15]	Nil
				Constipation/ileus	
				Neuropathy	Nil
				Chest pain	Nil

Risk factors and recommendation for prevention of SE	Recommendation for management of SE	In the elderly (≥65 years)	Metabolism	Excretion	Cross BBB
Elevated liver transaminases (>3x ULN) and bilirubin >1.5xULN Do not give therapy if neutrophil is count <1.5 × 109/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				
Risk factors include concurrent mitomycin	May respond to bronchodilators		Hepatic cytochrome P450 enzymes	Biliary	Brain and plasma levels are comparable in animal studies [16]
	Subacute pulmonary reactions characterized by cough, dyspnea, hypoxemia, and interstitial infiltration may respond to corticosteroid therapy, and oxygen may provide symptomatic relief				
Prior treatment with other neurotoxic chemotherapies 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				

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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
				Pain in tumor-containing tissue	Nil
Anthracyclines	Doxorubicin/ epirubicin [17, 18]	A/M	N/A	Cardiotoxicity: acute, chronic, and delayed	Cardiac assessment at baseline with clinical examination, ECG, and of LVEF assessment with radionuclide angiography (MUGA scan) or serial echocardiogram
		IV doses: 50–60 mg/m^2, 75–100 mg/m^2 3 weekly for doxorubicin and epirubicin, respectively, when used in combination			Once cumulative dose has surpassed 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

Risk factors and recommendation for prevention of SE	Recommendation for management of SE	In the elderly (≥65 years)	Metabolism	Excretion	Cross BBB
Nil	Acute pain syndrome within 30 min of infusion can occur at the tumor site after the first dose. It usually lasts from 1 h to several days. Management is with corticosteroids and narcotic analgesia, if necessary				
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	Doxorubicin: no information	Doxorubicin: in the liver and other tissues by an aldo-keto reductase enzyme	Doxorubicin: predominately bile	No
	The gold standard for diagnosis of anthracycline-induced cardiotoxicity is endomyocardial biopsy. However, it is rarely performed due to its invasive nature	Epirubicin: clearance may be decreased	Epirubicin: extensive hepatic metabolism also metabolized by other organs including RBC	Predominately hepatobiliary; rapid elimination of parent compound from plasma	
	Management of congestive cardiac failure This can include low-salt diet, diuretics, ACE inhibitors, or angiotensin receptor blockers, inotropes, and cardiac transplantation				
Prophylactic treatment for high-risk patients includes aggressive hydration and discontinuation of drugs that causes hyperuricemia (e.g., thiazide diuretics) or acidic urine (e.g., salicylates); monitor electrolytes and replace as required; alkalinize the urine, allopurinol/ rasburicase orally	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)				
Note: allopurinol can be given IV for patients not tolerating oral medications	Hemodialysis, if necessary				

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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
				Local extravasation	Monitor infusion site For patients with difficult venous access, consider central venous access device (CVAD) and contrast study

Risk factors and recommendation for prevention of SE	Recommendation for management of SE	In the elderly (≥65 years)	Metabolism	Excretion	Cross BBB
Ensure adequate peripheral access	Management of extravasation:				
Administration time 15–20 min	Stop the injection/ infusion and disconnect the intravenous tubing				
Monitor for erythematous streaking along vein and/or facial flushing	Withdraw as much of the drug as possible, via existing cannula or CVAD. Mark area of 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				

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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 [19]	M	EMA but not FDA approved indication	Acute infusion reactions	Monitor first infusion
		IV dose: mostly used at 40–45 mg/m^2 D1 q 4 weekly			
				Palmar-plantar erythrodysesthesia (PPE)	Monitor patient for symptoms (numbness or tingling)
				Stomatitis	Monitor patient for symptoms each cycle

Risk factors and recommendation for prevention of SE	Recommendation for management of SE	In the elderly (≥65 years)	Metabolism	Excretion	Cross BBB
Administer initial dose no faster than 1 mg/min	Slow or interrupt the rate of infusion	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
	Antihistamines				
	H2 blockers				
	Steroids				
If symptoms are present, consider increasing the dosing interval	Mild reactions resolve independently within 1–2 weeks				
Pyridoxine (50–150 mg/day) may be used for prophylaxis without affecting the antitumor activity Prophylactic corticosteroids may be of benefit [20]	More severe reactions may require a discontinuation of therapy, and corticosteroid use may assist in resolution				
Avoidance of skin stressor/pressure measures to decrease PPE following infusion (e.g., avoidance of tape on skin, sun exposure, hot water, pressure, or friction on skin)					
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				

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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
				Cardiotoxicity: acute, chronic, and delayed	Cardiac assessment at baseline with clinical examination, ECG and of LVEF assessment with radionuclide 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 [21]	M IV dose 60–75 mg/m^2 D1 q 3 weekly	First line in combination with cyclophosphamide	Cardiotoxicity	Cardiac assessment at baseline with clinical examination, ECG, and of LVEF assessment MUGA or serial echocardiogram

Risk factors and recommendation for prevention of SE	Recommendation for management of SE	In the elderly (≥65 years)	Metabolism	Excretion	Cross BBB
Occurs at lower frequency than conventional doxorubicin	Treatment for congestive heart failure is as per doxorubicin/ epirubicin				
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)					
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

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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
Antimetabolite	5-FU [22]/ capecitabine [23]	5-FU A Dose: mostly used as IV bolus 500–600 mg/m^2	Capecitabine monotherapy after failure of taxanes or anthracycline or where anthracyclines are contraindicated Capecitabine combination therapy: after failure of	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 and coronary angiogram)
		Capecitabine M	anthracycline-containing regimen	Capecitabine: palmar-plantar erythrodysesthesia (hand-foot skin reaction)	Nil
		Oral dose: 2,000–2,500 mg/m^2 divided equally between morning and evening D1-14 q 3 weeks		Hyperbilirubinemia	Monitor LFTs
Anti metabolite	Gemcitabine [24]	M (First line and beyond) IV dose: 1,000 mg/m^2 D1, 8 q 3 weekly	First line in combination with paclitaxel or single-agent palliative therapy	Elevated liver enzymes	Monitor LFTs

Risk factors and recommendation for prevention of SE	Recommendation for management of SE	In the elderly (≥65 years)	Metabolism	Excretion	Cross BBB
Patient screening	Risk factors include prior history of coronary artery diseases Management includes discontinuation of 5-FU/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				
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

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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
				Hemolytic uremic syndrome (HUS)	Monitor renal function and blood count
				Pulmonary toxicity	Nil
				Acute dyspnea and severe pulmonary toxicities (pulmonary edema, interstitial pneumonitis, and adult respiratory distress syndrome)	

Risk factors and recommendation for prevention of SE	Recommendation for management of SE	In the elderly (≥65 years)	Metabolism	Excretion	Cross BBB
Nil	Onset during and shortly after gemcitabine therapy (4–8 weeks postcompletion 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				

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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
				Fever/flulike symptoms	Nil
				Skin rash	Nil
				Vascular toxicity (thrombotic microangiopathy, veno-occlusive disease, and digital ischemic changes and necrosis)	Nil
Antimetabolite	Methotrexate [25]	A/M	Nil	Hepatotoxicity	Monitor LFTs
		IV dose: 40 mg/m^2 D1,8 q 4 weekly			
				Pulmonary toxicity: acute, subacute, or chronic (inflammation, pulmonary infections, and pulmonary lymphoma [27])	Nil
				Neurological toxicity (intrathecal and high-dose methotrexate)	Nil

Risk factors and recommendation for prevention of SE	Recommendation for management of SE	In the elderly (≥65 years)	Metabolism	Excretion	Cross BBB
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				
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 [26]
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 (IT) methotrexate	IT methotrexate				

(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

Risk factors and recommendation for prevention of SE	Recommendation for management of SE	In the elderly (≥65 years)	Metabolism	Excretion	Cross BBB
Aseptic meningitis: IT hydrocortisone or oral corticosteroids	Aseptic meningitis (onset hours): no treatment required. Patients can be rechallenged				
Transverse myelopathy: risk factors include frequent IT methotrexate and concurrent radiotherapy	Transverse myelopathy (onset hours–days): no specific intervention and recovery variable, and patients should not be rechallenged				
Leukoencephalopathy: risk factors include whole brain radiotherapy and IV methotrexate	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 24 h): 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	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	Cyclophosphamid [28]	A/M	Nil	Cardiac toxicity (ECG changes, elevation of cardiac enzymes, myocarditis, and myocardial necrosis)	Baseline ECG
		IV dose: 500–600 mg/m^2 D1 q 3 weekly			
		Oral dose: 100 mg/m^2 daily D1-14 q 4 weeks or 50 mg continuous daily dose			
				Hemorrhagic cystitis	Nil

Risk factors and recommendation for prevention of SE	Recommendation for management of SE	In the elderly (≥65 years)	Metabolism	Excretion	Cross BBB
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 [29]	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, and concurrent exposure to other urotoxic drugs or genitourinary radiotherapy	Discontinuation of cyclophosphamide, increase fluid intake, and maintenance of platelet count at >50,000/mm^3				
Encourage oral intake of fluids in 24–48 h prior to therapy and during therapy, frequent voiding. Drug administration should be completed early in the day to avoid the drug sitting in the bladder overnight	Cystitis				
Other measures include administration of mesna (rarely needed for doses <2 g/m^2), catheter bladder drainage, bladder irrigation, intravenous hydration with diuresis, and hyperhydration (not routinely recommended)	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				

(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	A/M	Nil	Immunogenicity: reduced skin test antigens (e.g., tuberculin-purified protein derivative)	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

Risk factors and recommendation for prevention of SE	Recommendation for management of SE	In the elderly (≥65 years)	Metabolism	Excretion	Cross BBB
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 nonreversible 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 antiinflammatories 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				

(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	Carboplatin [30]	A/M	Adjuvant HER2+ patients or metastatic	Myelosuppression (most commonly thrombocytopenia, but leukopenia, neutropenia, and anemia can also occur)	Monitor blood count
		IV dose: AUC 6			
				Hypersensitivity	
				Nephrotoxicity	Monitor renal function

Risk factors and recommendation for prevention of SE	Recommendation for management of SE	In the elderly (≥65 years)	Metabolism	Excretion	Cross BBB
Risk factors include prior chemotherapy, poor performance status, increasing age, impaired renal function, and concurrent myelosuppressive therapy	Anemia may be corrected with transfusions	Clearance may be reduced due to age-related renal function impairment	Intracellular	Renal	Yes
Dose-dependent and can be minimized by using the Calvert AUC-based dose formula	Dose as per Calvert AUC-based dose formula				
Risk associated with repeated exposure to platinum agents especially with a second course of platinum therapy	Treatment of 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				

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 another chapter in this volume. Chemotherapy regimens used in breast cancer have different potentials to induce emesis (Table 2.2) [32, 33].

Peripheral Neuropathy

Several classes of chemotherapy agents can induce peripheral neuropathy (CIPN) (see Table 2.1 for a detailed review of agents inducing neuropathy, as well as prevention and management of this side effect). Taxanes, ixabepilone, vinorelbine, and eribulin are the most likely cause of neuropathy in breast cancer patients. Comorbidities, such as diabetes and alcohol abuse, predispose patients to toxic nerve fiber damage from chemotherapy [34]. Common symptoms include burning sensation, tingling, loss of feeling, walking difficulties, trouble using fingers, poor balance, sensitivity to temperatures, loss of reflexes, and constipation. 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. 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.

Various small studies evaluating agents such as calcium, magnesium, vitamin E [35], glutamine [36], and glutathione [37] have been conducted mostly in oxaliplatin and cisplatin-based chemotherapy regimens. While the administration of intravenous calcium and magnesium in colon cancer patients receiving oxaliplatin appears to reduce the incidence of neuropathy while maintaining tumor response, more randomized controlled studies are required [38]. It is possible that pharmacogenetic studies will reveal particular genotypes at greater risk for CIPN [39].

See Table 2.1 for detailed management.

Table 2.2 Emetogenic potential of breast cancer chemotherapy agents

Level	Agents in breast cancer
High emetic risk (>90 % frequency of emesis without prophylaxis)	Combination doxorubicin/epirubicin with cyclophosphamide
	Cyclophosphamide IV >1,500 mg/m^2
	Doxorubicin > 60 mg/m^2
	Epirubicin > 90 mg/m^2
Moderate emetic risk (30–90 % frequency of emesis)	Carboplatin
	Cyclophosphamide IV ≤1,500 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-Flurouracil
	Gemcitabine
	Methotrexate >50 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

Adapted from [32, 33]

Cardiac Failure

Anthracyclines are highly effective drugs in breast cancer but have the significant drawback of inducing cardiac failure. 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 [40]

Due to the risk of cardiomyopathy, a lifetime maximum dose places limits on continued anthracycline administration (see Table 2.1). Acute, chronic, and delayed cardiotoxicities have 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. It is usually transient and does not require treatment intervention. Rarely, pericarditis, myocarditis, or cardiac failure occurs [41]. Chronic cardiac toxicity, in the form of irreversible cardiomyopathy, is dose-related and indolent in onset. It generally presents within 1 year of treatment with signs and symptoms of reduced left ventricular ejection fraction. Delayed cardiotoxicity occurring many years after exposure to anthracycline is also described and thought to be dose-related and irreversible. Table 2.1 describes the management of anthracycline-induced cardiac failure.

Cardiotoxicity may occur at lower doses in patients with prior mediastinal/pericardial irradiation, concomitant use of other cardiotoxic drugs, doxorubicin exposure at an early age, and advanced age [42]. Data also suggest that preexisting heart disease is a cofactor for increased risk of anthracycline cardiotoxicity. Coadministration with anti-HER2 agents is associated with increased risk of cardiotoxicity and is discussed further in this chapter [43].

Several approaches to reduce the cardiotoxicity of anthracyclines have been investigated. Anthracycline damage is presumed to result from the formation of anthracycline-iron complexes within myocardial cells. Dexrazoxane, a chelating agent, binds iron intracellularly. It is also thought to extract iron

from the anthracycline-iron complexes [44]. Unfortunately, a phase III trial evaluating this agent in 682 patients with advanced breast cancer therapy revealed a lower objective response rate (46.8 % vs. 60.5 %, 95 % CI: –25 % to –2 %; P=0.019) [45]. ASCO guidelines 2008 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 [46].

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 [42]. A third approach consists in prolonging the anthracycline infusion time: nonrandomized data from MD Anderson Cancer Center strongly suggest a cardioprotective effect in delivering anthracyclines as a 96-h infusion versus bolus doses [47].

Two novel anthracyclines deserve specific mention owing to their reduced cardiac toxicity profile: pegylated liposomal doxorubicin (PLD) and non-pegylated liposomal doxorubicin (non-PLD). Studies in the first-line setting have shown better cardiac toxicity profile with similar antitumor effects for both agents [48, 49].

Gastrointestinal Side Effects: Mucositis, Diarrhea, and Constipation

Diarrhea is a side effect of certain chemotherapy agents such as 5-fluorouracil (5-FU) and capecitabine. Diarrhea is associated with fluid and electrolyte loss as well as a decrease in 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 parasitic, or viral pathogens. Abdominal imaging, as well as occasionally

endoscopy, may be indicated to rule out confounding causes of diarrhea.

Treatment guidelines for patients with chemotherapy-induced diarrhea have been published [50]. 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 [51]. Pharmacological therapies for chemotherapy-induced diarrhea involve agents such as loperamide [52]. Other agents that show benefit include opioids and octreotide [53]. 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-FU, capecitabine, and methotrexate. Factors that may predict for oral mucositis are previous episodes of mucositis with previous treatment cycles. It is associated with a higher risk of infection and can severely compromise nutrition and quality of life [54]. Treatment is mostly supportive, with good oral hygiene, mouthwashes, and analgesia [55]. Small trials with agents such as glutamine [56], AES-14 [57], and various growth factors [58–60] have been explored with inconclusive results. Athermic laser is effective in the prevention and management of mucositis [61].

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.

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.” Patients often describe a vagueness and difficulty in planning. 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 [62]. 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 [63–65]. This has been seen in breast cancer patients, and a study by Ahles et al. also described a dose-dependent effect with more cycles of chemotherapy linked to lower neuropsychological scores [66]. Cognitive dysfunction can persist for years after the completion of chemotherapy, and 5-FU has been implicated as a potential agent [67, 68]. To date there are no therapies for the prevention or management of this side effect. Patients and caregivers need to be educated about its occurrence, and behavioral modifications need to be encouraged

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 [69, 70]. Women who undergo radiation therapy may be influenced by radiation tattoos, fatigue, or changes in breast sensation and arm mobility [71]. Chemotherapy has also been associated with sexual dysfunction [72]. In a study of 100 women, sexual dysfunction attributed to breast cancer or its treatment was assessed via a validated questionnaire, the female sexual function index (FSFI), and defined as an FSFI score <26. Sexual dysfunction was reported by 75 % of the responders. Patients attributed their sexual dysfunction to chemotherapy in 83 % of cases. Other contributors to sexual dysfunction were felt to include anxiety (by 83 % of the patients) and change in relationship with a partner (by 46 % of patients).

Assessment of sexual symptoms throughout treatment and beyond may facilitate the use of potential and specific interventions [73].

Fertility

Adjuvant chemotherapy for breast cancer may render a premenopausal patient either temporarily or permanently amenorrheic, thus affecting her fertility. For premenopausal women this can be a significant concern, causing distress and affecting treatment-related decisions. Six hundred fifty-seven young women with breast cancer were surveyed in regards to fertility concerns; 57 % recalled substantial concern at diagnosis about becoming infertile with treatment, while 29 % of women reported that infertility concerns influenced treatment decisions [74]. Several options for potential preservation of fertility exist, such as ovarian tissue or embryo cryopreservation and luteinizing-hormone-releasing hormone agonists administered during chemotherapy. They are discussed in Chap. 14. Patients should be referred for fertility counseling to a multidisciplinary environment.

Secondary Malignancies

Adjuvant chemotherapy with anthracyclines and/or alkylating agents has been implicated as risk factor for the development of secondary malignancies, mostly acute myeloid leukemia (AML) with or without preleukemic myelodysplastic syndrome (MDS). Often the benefit of preventing relapse from an already existing malignancy overrides the small numbers of patients that will go on to develop a second malignancy. A Danish survey [75] identified five cases of AML in 360 patients treated with epirubicin/cyclophosphamide, epirubicin/cisplatin, or alkylating agents. In a meta-analysis of 19 randomized [76] controlled trials ($N = 9{,}796$) 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. Therefore, patients who receive standard doses of chemotherapy have a relatively low risk of AML/MDS.

Endocrine Therapies

Endocrine therapy is the first "targeted" medical treatment in oncology with antitumor activity restricted to patients whose breast tumors express estrogen receptors (ERs) and/or progesterone receptors (PRs). 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:

1. The selective estrogen receptor modulators (SERMs), which bind the ER and interfere with its transcriptional activity
2. The selective estrogen receptor downregulator fulvestrant, which binds the ER and accelerates its destruction
3. 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 SERMs 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 has no additional benefit in terms of overall survival and only modestly improves disease-free survival [77, 78]. 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, the uterus, and the cardiovascular system.

Fulvestrant (Faslodex, AstraZeneca, Wilmington, DE, USA) 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 [79].

Third-generation *aromatase inhibitors* (AIs) (exemestane, anastrozole, and letrozole) have shown superior control of advanced breast cancer when compared to tamoxifen, but no significant impact on overall survival. 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 [80–83]. Their impact on overall survival, however, is of small magnitude. Aromatase inhibitors are prescribed today to many postmenopausal patients newly diagnosed with hormone receptor-positive operable breast cancer, particularly when their risk of relapse is from moderate to high. Their optimal timing and duration has not yet been fully elucidated.

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 disease with slightly different side effect profiles [84]. 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. Clinical fracture rates were similar in both study arms, however. The FACE trial comparing – head-to-head – letrozole and anastrozole in about 4,000 women with ER-positive, node-positive breast cancer should also release its results soon.

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, which is 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 (two trials of a few thousand patients). For fulvestrant, comparisons to either tamoxifen or AIs are available only in the context of smaller randomized metastatic trials involving a few hundred patients [85–87]. These toxicities are described in Table 2.3 and are discussed in more detail below.

Gynecologic 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. Fewer gynecologic symptoms have been reported with fulvestrant than with tamoxifen (3.9 % vs. 6.3 %) [85]. Aromatase inhibitors are devoid of endometrial side effects, and it is therefore not surprising that gynecologic 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 [80, 81]. Fewer gynecologic 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 [81, 82]. 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 [88]. 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, 52 women had to undergo hysteroscopy and curettage, resulting in four uterine perforations [89]. Therefore, routine annual gynecologic

TABLE 2.3 Side effects of endocrine agent therapy

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
			Gynecologic 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

Aromatase inhibitors	Adjuvant metastatic	Presence of hormone receptors in primary tumor	Arthralgias and myalgia		Consider pain and antiinflammatory 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
Anastrozole 1 mg PO daily			Bone loss	Bone mineral density measurement by DEXA 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
Letrozole 2.5 mg PO daily			Cardiovascular events		Regular screening for cardiovascular risk factors such as hypertension and hypercholesterolemia
Exemestane 25 mg PO daily			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
Fulvestrant 500 mg IM d0, d15, d28 then q 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 antiinflammatory medications
					Encourage patients to do regular physical exercise
			Thromboembolic events		Interrupt fulvestrant for a few weeks in case of surgery/ immobilization
					Consider prophylactic anticoagulant if ≥4-h airplane travel
			Hot flushes		Consider antidepressants such as venlafaxine or the centrally acting alpha-adrenergic agonist, clonidine

examination is the preferred method of monitoring 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 [90]. Aromatase inhibitors in this case are an alternative for postmenopausal women, but they induce vaginal dryness, contributing to the loss of libido. Nonhormonal lubricants may be used to release symptoms. Due to the risk of systemic absorption, estrogen-containing vaginal preparations should be avoided.

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 [80–83]. 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 develop this toxicity. Therefore, women harboring this genetic alteration are not candidates for tamoxifen [91]. 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 of the following screening blood tests: resistance to activated protein C, antiphospholipid antibodies, antithrombin, and proteins C and S. Genotyping for factor V and prothrombin can be useful but should be discussed beforehand with the patient.

In the head-to-head comparison between fulvestrant and tamoxifen, the risk of developing venous thromboembolic events was comparable with both treatments [85]. Thus, in women treated with fulvestrant, the same preventive measures should be considered as in those who are treated with tamoxifen.

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 noncompliance. This adverse event seems to occur slightly more often in patients treated with tamoxifen compared to AIs in adjuvant trials and compared to fulvestrant in treatment of metastatic disease. The reported incidence across different studies is around 35–40 % [80–83]. Successful management is challenging. Nonestrogenic 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 in a recent trial [92].

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 % [93]. 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 [94].

Musculoskeletal Pain

According to toxicity data of multiple adjuvant trials, joint pain emerged as a prominent side effect of AIs, seen in about 35 % of women and representing the first cause of noncompliance. 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 antiinflammatory drugs (NSAIDs), cyclooxygenase-2 inhibitors, and the use of pain medications such as opioids can help to release symptoms [95]. 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.

Bone Loss

Estrogen deprivation at almost undetectable levels by AIs leads to an increased bone loss and an increased risk of fractures. This is in sharp contrast to 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 [80, 83]. 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 [82, 83].

The reported fracture rate with 5 years of AI in the adjuvant setting ranges from 5 to 11 % [80, 81, 83]. Regarding fulvestrant, osteoporosis was only reported in one patient receiving the dose of 500 mg [79].

It is highly recommended that all women starting treatment with an AI undergo a bone mineral density (BMD) measurement by dual-energy x-ray absorptiometry (DEXA) 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 [96]. 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 (1,200–1,500 mg/day) should be considered to preserve bone health [97]. Current ASCO guidelines recommend the initiation of bisphosphonate treatment in the case of osteoporosis (T score ≤ 2.5) [96]. 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 [98].

Cardiovascular Events

Cardiovascular events include myocardial ischemia and strokes. Monitoring of the cardiovascular safety of aromatase inhibitors has been poorly standardized in trials; 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 [80, 81]. However, a recent meta-analysis of seven adjuvant trials including 30,023 patients found that the risk of cardiovascular disease (including myocardial infarction, angina, and cardiac failure) was significantly higher with AIs upfront compared to 5 years of tamoxifen or the switching strategy (4.2 % in the AI group vs. 3.4 % in the tamoxifen group, OR = 1.26, 95 % CI = 1.10–1.43, $P < 0.001$) [99]. There is no evidence that tamoxifen increases the risk of ischemic heart disease compared to placebo in NSABP-P1 trial. Severe coronary syndromes ranged from 0.94 to 1.12 % in this study [93]. 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 AIs. 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.

Cognitive Dysfunction

Data from large adjuvant trials regarding cognitive function are 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 [100]. 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 [101]. These data are still too limited and immature to draw firm conclusions and to make recommendations on how cognitive function impairment should be monitored during long-term hormonal treatment.

Targeted Agents

Trastuzumab (Herceptin, Genentech, South San Francisco, CA, USA) is a monoclonal IgG1 class humanized murine antibody that binds the extracellular portion of the HER2 transmembrane receptor [102]. Since its launch in 1998, trastuzumab has become the backbone of care of HER2 amplified breast cancer, both in the metastatic and early disease settings [103–108].

In 2007, a second targeted agent was approved for the treatment of HER2-positive breast cancer: lapatinib (Tykerb, GlaxoSmithKline, Philadelphia, PA, USA). 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 is currently evaluated in clinical trials in the adjuvant setting [109, 110].

A growing list of novel anti-HER2 agents is showing promising activity in women with HER2-positive disease. Pertuzumab is a monoclonal antibody that binds to the HER2 dimerization domain [111] and, as a result, inhibits the formation of HER2 dimers, including the HER2/HER3 heterodimer. Trastuzumab DM-1 is an antibody-drug conjugate linking trastuzumab with the fungal toxin maytansine (DM-1) that specifically delivers the antimicrotubule agent (DM-1) to HER2-positive cells [112]. Neratinib (HKI-272) is a potent irreversible pan-HER kinase inhibitor with efficacy shown in HER2-positive metastatic breast cancer [113]. Afatinib (Tomtovok, Boehringer Ingelheim, Ridgefield, CT, USA) is an oral, irreversible inhibitor of HER1/HER2 and is in trials in HER2-positive metastatic tumor breast cancer [114–116].

Of note, recent trials have shown promising results with "dual HER2 blockade" involving trastuzumab with either lapatinib [117] or pertuzumab [118].

Bevacizumab (Avastin, Genentech, South San Francisco, CA, USA) is the third targeted agent approved for the treatment of metastatic breast cancer. Bevacizumab is a humanized monoclonal antibody against vascular endothelial growth factor (VEGF), which is a key angiogenic factor [119]. Bevacizumab is approved by EMA for the first-line treatment of metastatic breast cancer in combination with paclitaxel or capecitabine.

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 to have 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 lead 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, in contrast to monoclonal antibodies, which 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 lesser extent, myocardial dysfunction.

Table 2.4 summarizes the indications of targeted agents used in the treatment of breast cancer [51, 120–151], major side effects, and monitoring tests. Management algorithms for some key toxicities are presented in Figs. 2.1, 2.2, and 2.3.

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 breast cancer [103]. 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 [103–106]. Even though its causes are not fully elucidated,

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 mg/kg 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 fully healed Exclude patients with nonhealing 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

(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
Bevacizumab	Metastatic breast cancer in combination with paclitaxel or capecitabine	Bleeding/ hemorrhage	0.4–5.4 %	Clinical appreciation	Do not exclude patients with CNS metastases
				CBC	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 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 Bevacizumab does not appear to elevate the risk compared to chemotherapy	Clinical appreciation, x-ray, and CT scan	

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

(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
Pertuzumab	Ongoing trials in HER2-positive (IHC 3+ or IHC 2+ and FISH ratio >2.2) breast cancer	Asymptomatic left ventricular systolic dysfunction	6.9 % with pertuzumab alone, 3.4 % with pertuzumab in combination with non-anthracycline chemotherapy, and 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, and 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 complaint. NCI-CTC grading.	Supportive measures. Loperamide if necessary.
		Nausea	24–27 %, no grade 3 or 4. 27 % when given with trastuzumab.	Patient complaint	Antiemetics at the discretion of the treating physician
		Fatigue	22–24 %, 2.4 % grade 3. 33 % when given with trastuzumab.	Patient complaint	
		Rash including allergic reaction	20 %, no grade 3 or 4	Clinical complaint	
		Vomiting	15 %, 2.5 % grade 3	Patient complaint	Antiemetics at the discretion of the treating physician

T-DM-1	Ongoing trials in HER2-positive (IHC 3+ or IHC 2+ and FISH ratio >2.2) breast cancer	Thrombocytopenia	8 % grade 3 or 4	CBC before administration	Dose reductions from 3.6–3 mg/kg then 2.4 mg/kg
		Fatigue	4.5 % grade 3 or 4. 65.2 % all grades	Patient complaint	
		Nausea	0.9 % grade 3 or 4. 50.9 % all grades		Antiemetics at the discretion of treating physician
		Headache	40.2 % grade1		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
Lapatinib	Metastatic HER2-positive (IHC 3+ or IHC 2+ and FISH ratio >2.2) breast cancer in combination with capecitabine after progression on trastuzumab	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 complaint. 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, and 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 complaint. 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 complaint	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 complaint	Antiemetics 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 complaint	
		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 complaint. 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

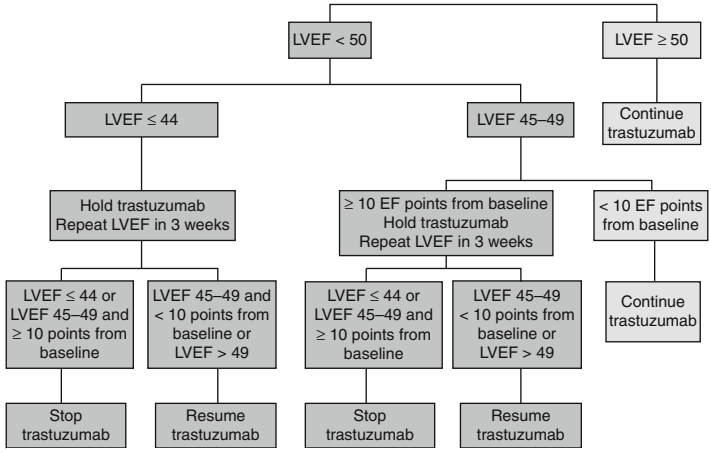

FIGURE 2.1 Management of patients showing cardiac dysfunction on trastuzumab (Reprinted from Suter et al. [152]. Reprinted with permission. © 2007 American Society of Clinical Oncology. All rights reserved)

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 and potentially reversible with medical therapy, and rechallenge is possible [153]. Potential risk factors influencing LVEF deterioration are older age, hypertension, and a baseline LVEF in the lower normal range [43, 103, 154]. Algorithms for initiation of therapy are proposed, as well as algorithms for monitoring and managing cardiac events (Fig. 2.1). Reporting of cardiac events in trastuzumab trials prompted close cardiac monitoring of patients on lapatinib, neratinib, and afatinib. Incidence of cardiotoxicity was found to be less with these agents, even in patients pretreated with trastuzumab and anthracycline. Furthermore, most LVEF decreases were asymptomatic and

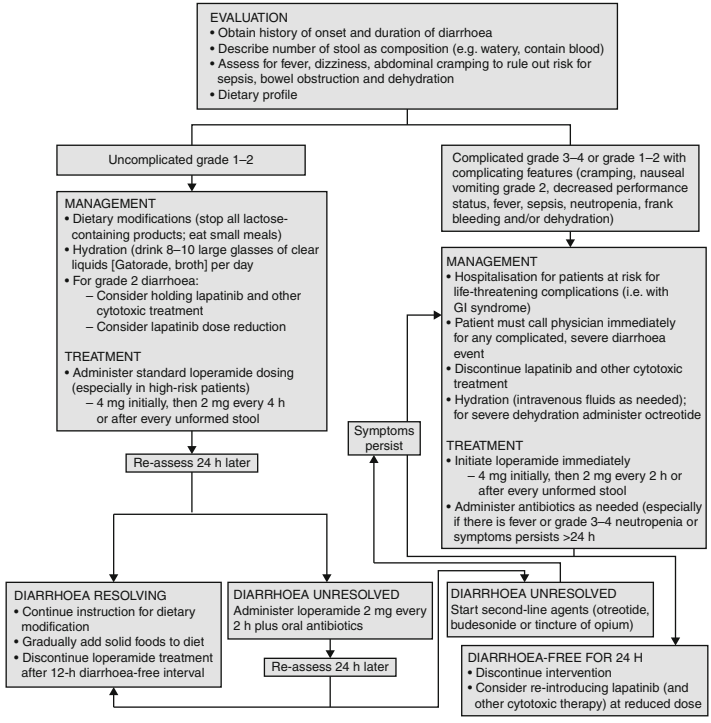

FIGURE 2.2 Management of patients experiencing diarrhea on HER1/HER2 tyrosine kinase inhibitors (Modified from [146])

almost universally reversible [150]. 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 [155].

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 [156]. A meta-analysis of bevacizumab trials in metastatic breast cancer demonstrated the increased incidence of congestive heart failure (CHF) in bevacizumab-treated

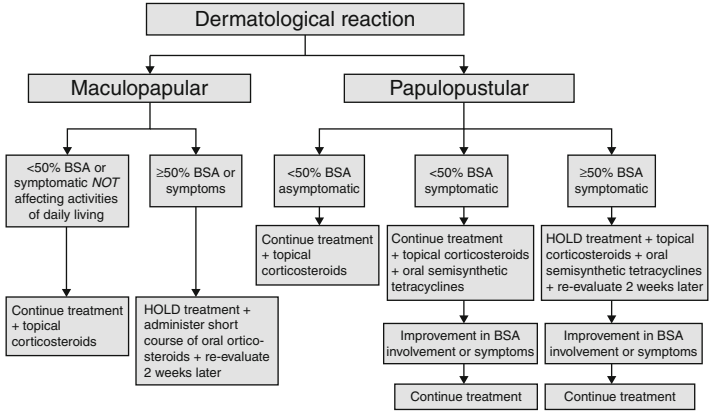

FIGURE 2.3 Management of patients experiencing skin toxicity on HER1/HER2 tyrosine kinase inhibitors (Modified from [146])

patients when compared to controls. The overall incidence, however, remains low and is not dose-dependent; nor is it associated with type of concomitant chemotherapy. Early available data show recovery of cardiac function with interruption of treatment and introduction of cardiac medications [136]. Bevacizumab is also responsible for rare arterial and venous thromboembolic events [133].

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 [157]. 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 [126].

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, and so forth. 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 produces one of the highest incidences of infusion reactions among the monoclonal antibodies, but these reactions are largely mild to moderate. Most patients are rechallenged successfully, with permanent discontinuation considered only 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 [158]. However, there are 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, intravenous antihistamines, bronchodilators, oxygen, and vasopressors should be readily available.

Hepatotoxicity

Hepatobiliary adverse events (AEs) have been reported in patients treated with lapatinib. Hepatotoxicity is predominately hepatocellular injury [148]. 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's Law criteria [149]. One study reported four withdrawals from treatment and one toxic death by hepatic failure in 138 patients treated with lapatinib [159].

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 [160]. Furthermore, recent pharmacogenetic evaluations have identified associations between lapatinib-induced liver injury and 4 MHC class II alleles. A strong statistical association was observed with HLA-DQA1*02:01 [148]. 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 [161], and LFT elevations should alert one to possible liver toxicity of all small molecules used in breast cancer, including neratinib and afatinib.

Gastrointestinal Perforation, Wound-Healing Complications, and Bleeding

Gastrointestinal perforation, wound-healing complications, and bleeding 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.

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 and treatment discontinuations, and thus decreased

efficacy of these small molecules [161]. 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 and afatinib. The pathophysiological mechanism is secretory by inhibition of EGFR effects on chloride secretion [162]. Biopsy does not 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 [163].

Dual HER2 blockade, using either trastuzumab and lapatinib or trastuzumab and pertuzumab, exacerbates diarrhea, which needs prompt and aggressive treatment. An algorithm (see Fig. 2.2) initially developed for management of chemotherapy-induced diarrhea is applicable once diarrhea occurs under pan-ERB TKI's therapy [50].

Skin Rash

Skin rash has been described as a class effect toxicity of ErbB1 targeting agents. As lapatinib and afatinib target 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 [164]. 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, resolve spontaneously, and 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 (see Fig. 2.3) has been developed [147, 165]. There is no clear evidence that the occurrence and severity of rash associated with agents used in breast cancer is correlated with tumor response or disease outcome, as is suggested with other anti-EGFR molecules such as cetuximab, erlotinib, and gefitinib [166, 167]. Further details on skin toxicity are considered elsewhere in this book.

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 [168]. The majority of cases were described later on with anti-EGFR tyrosine kinase inhibitors mostly used in non-small cell lung cancer, namely, erlotinib [169, 170] and gefitinib [171], as well as with mTOR inhibitors such as everolimus. Few cases were fatal [171], and the majority recovered with treatment interruption and corticosteroids [172]. Rechallenge is possible [171]. 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 [173]. Diagnosis is one of exclusion because symptoms mimic congestive heart failure, infection, and lymphangitic carcinomatosis. Fortunately, this complication is 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 (7/4,283) developing pulmonary events: three patients experienced pneumonitis, two interstitial lung disease, and two lung infiltrations. Incidence of lapatinib-related interstitial pneumonitis is 0.3 % (36/12,795) in the overall lapatinib program [174]. All cases were reversible. Other studies with lapatinib, neratinib, and afatinib report mainly episodes of dyspnea but not interstitial lung disease specifically. One phase 1 study with afatinib [175] reported one episode of reversible pneumonitis in 53 patients. Even though TKI-induced pneumonitis is rare in breast cancer patients, it is a potentially dangerous complication that needs early recognition and management.

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 – for example, in young women on a LHRH agonist combined with either tamoxifen or anastrozole in postmenopausal women older than 55 years on adjuvant endocrine therapy [176–178].

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 [179, 180]. 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 [181]. The possible antimetastatic role of denosumab is currently under investigation.

Bisphosphonates and RANKL monoclonal antibodies have common toxicities with different incidences, which are reviewed in detail in Chap. 16.

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