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

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

Keywords

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

2.1 Introduction

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

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

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

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

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

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

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

2.2 Chemotherapy

2.2.1 Classes of Chemotherapy and General Toxicities

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

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

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

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

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

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

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

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

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

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

2.2.1.4 Alkylating Agents (Cyclophosphamide, Cisplatin, and Carboplatin)

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

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

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

2.2.1.5 Dose-Dense Chemotherapy

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

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

Table 2.1 Side effects of chemo_2016 update

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

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

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

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

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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
Alkylating agents	Cyclophosphamide	Adjuvant or metastatic		Immunogenicity: reduced skin test antigens (e.g., tuberculin purified protein derivative)	Nil
			Nil	Interstitial fibrosis	Nil
				Nasal stuffiness or facial discomfort	Nil
				Radiation recall reaction	Nil
				SIADH	Nil
				Secondary malignancies	Nil
				Fluid retention and dilutional hyponatremia	Nil
Alkylating agents	Carboplatin[z]	A/M IV dose: AUC 6	Adjuvant HER2+ patients or metastatic	Myelosuppression (most commonly thrombocytopenia, but leukopenia, neutropenia, and anemia can also occur)	Monitor blood count
				Hypersensitivity	
				Nephrotoxicity	Monitor renal function

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

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Table 2.1 (continued)

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

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

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Table 2.1 (continued)

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

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

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Table 2.1 (continued)

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

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

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Table 2.1 (continued)

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

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

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Table 2.1 (continued)

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

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

(continued)

Table 2.1 (continued)

[a]Squibb BM: Taxol® product monograph

[b]Sanofi: Docetaxel product monograph

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

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

[e]Celgene: Abraxane product monograph

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

[g]Squibb BM: Ixempra® product monograph

[h]Eisai: eribulin product monograph

[i]Pharmaceuticals PF: Navelbine® product monograph

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

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

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

[n]Medicines TP: Doxorubicin product monograph

[m]Medicines TP: Epirubicin product monograph

[o]Janssen: Caelyx® product monograph

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

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

[r]Information OF: 5-fluorouracil product information

[s]Genentech: Xeloda® product monograph

[t]Lilly: Gemzar® product monograph

[u]Pfizer: Methotrexate product monograph

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

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

[x]Squibb BM: Cytoxan®

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

[z]Information OF: Carboplatin product information

2.2.2 Incidence and Management of Selected Chemotherapy Toxicities

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

2.2.2.1 Febrile Neutropenia

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

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

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

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

2.2.2.2 Management of Chemotherapy-Induced Emesis

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

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

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

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

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

2.2.2.3 Peripheral Neuropathy

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

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

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

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

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

2.2.2.4 Cardiac Failure

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

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

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

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

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

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

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

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

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

2.2.2.5 Gastrointestinal Side Effects: Mucositis, Diarrhea, and Constipation

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

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

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

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

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

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

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

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

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

2.2.2.6 Cognitive Dysfunction

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

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

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

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

2.2.2.7 Altered Body Image and Sexual Dysfunction

Other less recognized effects of chemotherapy include sexual dysfunction.

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

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

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

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

2.2.2.8 Fertility

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

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

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

2.2.2.9 Secondary Malignancies

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

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

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

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

2.3 Endocrine Therapies

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

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

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

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

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

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

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

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

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

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

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

2.3.1 Gynecological Side Effects

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

Table 2.3 Side effects of endocrine therapies

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

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

(continued)

Table 2.3 (continued)

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

2.3.2 Thromboembolic Disease

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

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

2.3.3 Hot Flashes

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

2.3.4 Eye Problems

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

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

2.3.5 Musculoskeletal Pain

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

2.3.6 Bone Loss

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

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

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

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

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

2.3.7 Cardiovascular Events

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

2.3.8 Cognitive Dysfunction

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

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

2.4 Targeted Agents

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Table 2.4 Side effects of targeted agents

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

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

(continued)

Table 2.4 (continued)

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

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

(continued)

Table 2.4 (continued)

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

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

(continued)

Table 2.4 (continued)

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

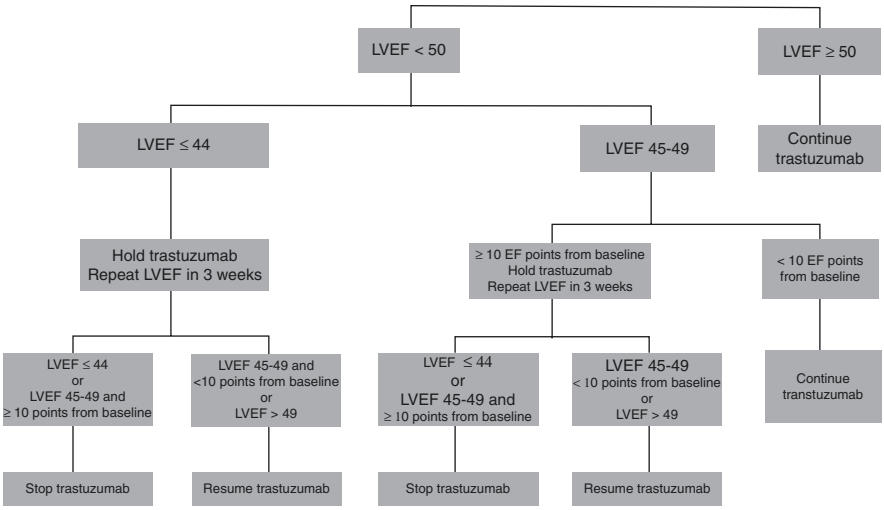

Fig. 2.1 Management of patients showing cardiac dysfunction on trastuzumab [162]

2.4.1 Cardiovascular Toxicity

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

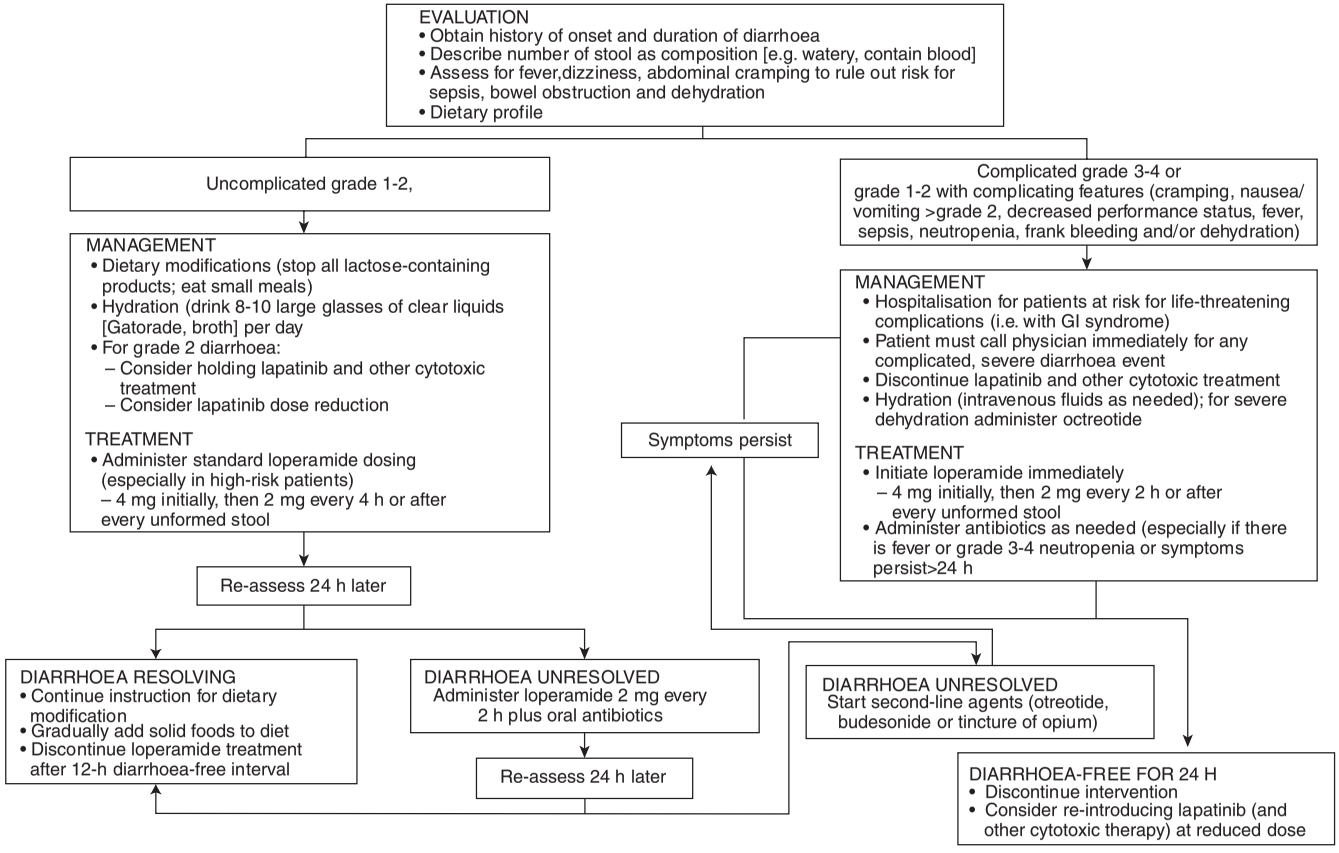

Fig. 2.2 Management of patients experiencing diarrhea on HER1/HER2 tyrosine kinase inhibitors [156]

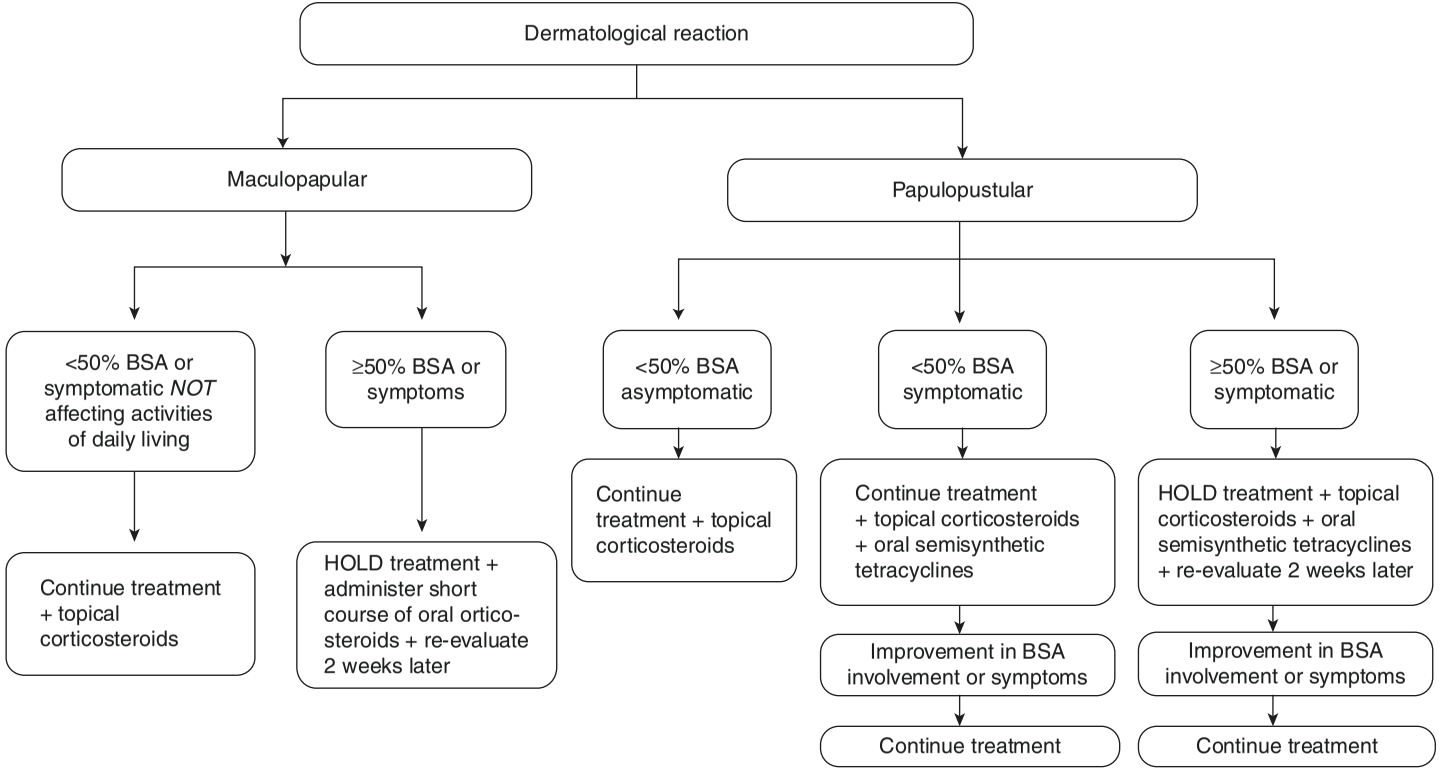

Fig. 2.3 Management of patients experiencing skin toxicity on HER1/HER2 tyrosine kinase inhibitors [156]

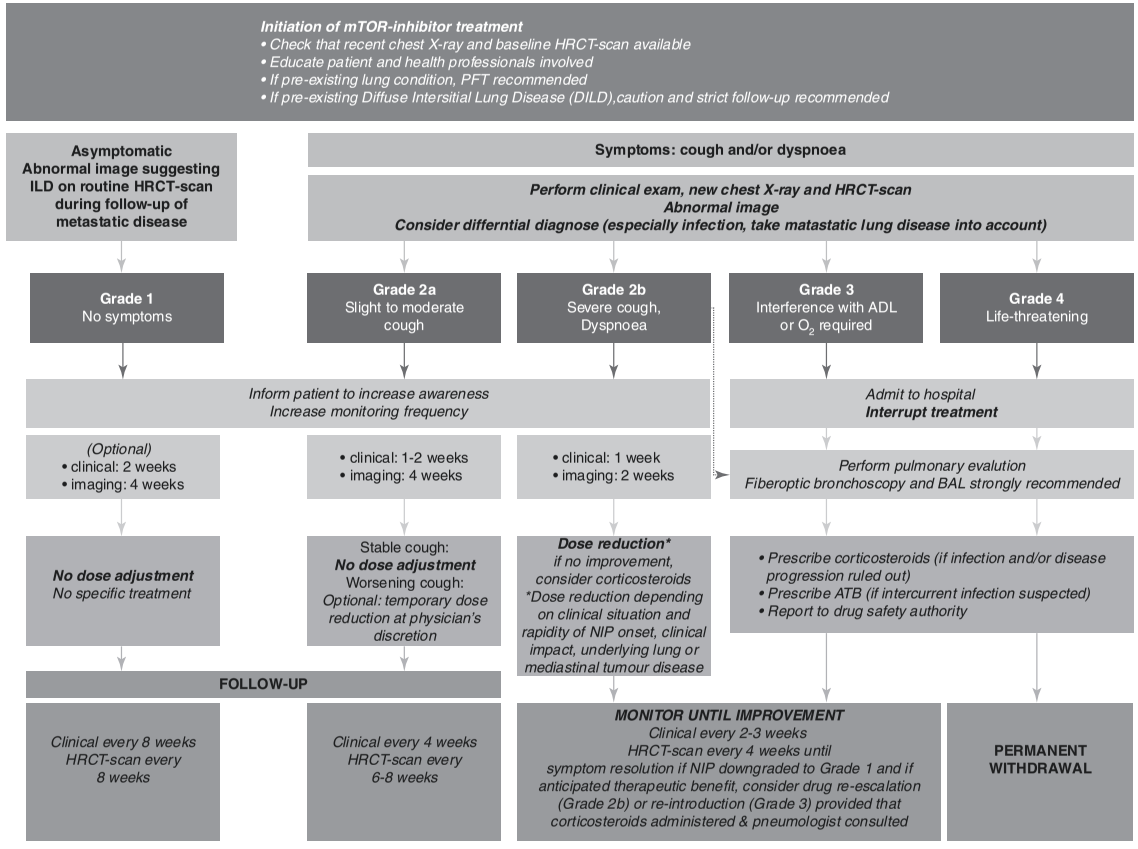

Fig. 2.4 Management of patients experiencing interstitial pneumonitis on mTOR inhibitors [187]

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

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

2.4.2 Hypertension

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

2.4.3 Infusion Reactions

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

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

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

2.4.4 Hepatotoxicity

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

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

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

2.4.5 Gastrointestinal Perforation, Wound-Healing Complications, and Bleeding

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

2.4.6 Diarrhea

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

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

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

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

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

2.4.7 Skin Rash

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

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

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

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

2.4.8 Interstitial Pneumonitis

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

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

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

2.4.9 Hematological Toxicity

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

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

2.5 Bone-Modifying Agents

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

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

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

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

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