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After reading the article "Understanding, Recognizing, and Managing Toxicities of Targeted Anticancer Therapies," the learner should be able to:

1. Describe common side effects of targeted anticancer therapies and recommendations for their management.

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Understanding, Recognizing, and Managing Toxicities of Targeted Anticancer Therapies

Grace K. Dy, MD[1]; Alex A. Adjei, MD, PhD[2]

Advances in genomics and molecular biology have identified aberrant proteins in cancer cells that are attractive targets for cancer therapy. Because these proteins are overexpressed or dysregulated in cancer cells compared with normal cells, it was assumed that their inhibitors will be narrowly targeted and relatively nontoxic. However, this hope has not been achieved. Current targeted agents exhibit the same frequency and severity of toxicities as traditional cytotoxic agents, with the main difference being the nature of the toxic effects. Thus, the classical chemotherapy toxicities of alopecia, myelosuppression, mucositis, nausea, and vomiting have been generally replaced by vascular, dermatologic, endocrine, coagulation, immunologic, ocular, and pulmonary toxicities. These toxicities need to be recognized, prevented, and optimally managed. **CA Cancer J Clin 2013;63:249-279. ©2013 American Cancer Society, Inc.**

Keywords: toxicity, targeted agents, mechanism-based toxicity, off-target toxicity, therapeutic index, kinase inhibitors, immunotherapeutic agents

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Introduction

The development of a large number of targeted therapies for cancer in the past decade has led to new mechanism-based adverse effects of new drug classes that affect virtually every organ system in the body. Early termination of the clinical development of some of these drugs was prompted by unanticipated toxicities. Moreover, the majority of these agents are administered in a continuous fashion, thus making cumulative toxicities a common event. A recent meta-analysis of randomized clinical trials with targeted agents showed what many individual studies have reported: that alongside the improvement in survival outcomes, treatment discontinuation due to toxicity and toxic deaths was greater for these new agents compared with control groups.[1] Thus, for targeted therapies with demonstrable clinical anticancer efficacy, treating physicians have to be cognizant of the insidious onset of subacute to late toxicities associated with chronic use of these agents. This article aims to provide a succinct overview of toxicities, associated with novel agents (excluding radiopharmaceuticals and antibody–drug conjugates), and relevant implications for the management of patients. The targets and associated toxicities discussed in the following sections are graphically depicted in Figures 1 (signal transduction targets) and 2 (immunologic targets).

Mechanism-Based Toxicities

On-target toxicities, such as rash associated with inhibitors of the epidermal growth factor receptor (EGFR) signaling pathway or hypertension with inhibitors of the vascular endothelial growth factor receptor (VEGFR) signaling pathway are "class effects" and therefore difficult to prevent by designing different active molecules and thus need to be managed proactively. By definition, these mechanism-based toxicities are shared by all agents that reliably inhibit a specific target. Off-target toxicities are generally observed when therapeutic agents inhibit other unintended targets. Typically, these "off-targets" share structures or residues with the intended targets. Although these toxicities can be minimized by structural drug design to increase selectivity towards the main target, it is likely that in many instances, complete selectivity is either not feasible or even desired (eg, eliminating platelet-derived growth factor receptor (PDGFR) from a c-KIT inhibitor narrows the spectrum of clinical activity in gastrointestinal tumors). Due to cross-interaction of multiple pathways, toxicities can overlap,

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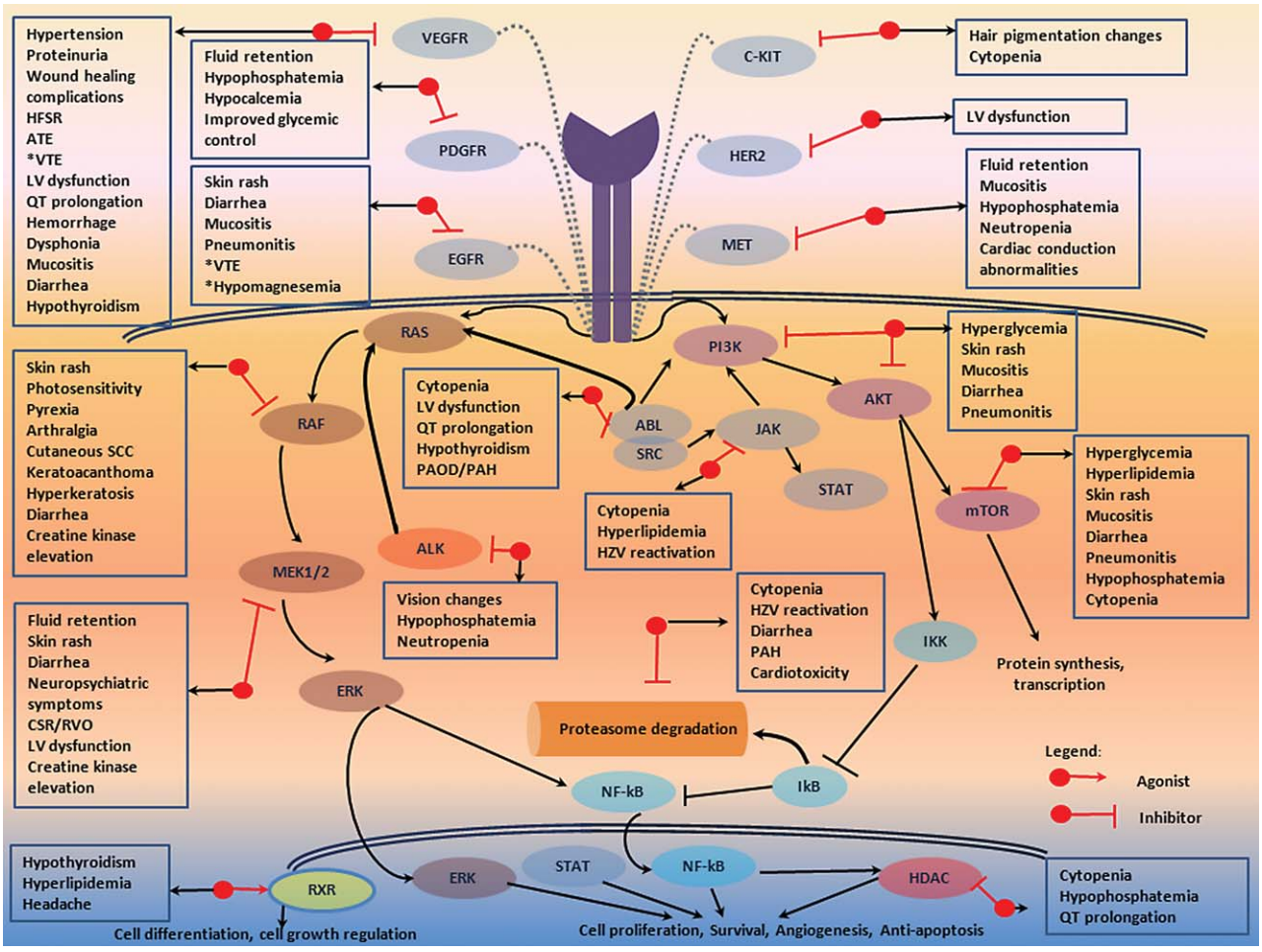

FIGURE 1. Toxicities Associated With Signal Transduction Inhibitors.*Associated predominantly with monoclonal antibodies. ATE indicates arterial thromboembolism; CSR, central serous retinopathy; HZV, herpes zoster virus; LV, left ventricular; PAH, pulmonary arterial hypertension; PAOD, progressive arterial occlusive disease; RVO, retinal vein occlusion; SCC, squamous cell cancer; VTE, venous thromboembolism.

whether arising from on- or off-target mechanisms. Moreover, these toxicities can manifest in a wide variety of tissues and organs. Table 1 provides a summary of the frequency and suggested management of adverse effects, both on- and off-target, arising from various classes of targeted therapies discussed below.

Dermatologic

Cutaneous adverse effects are manifested by a wide variety of inhibitors of signal transduction proteins including the EGFR, RAS/RAF/ERK, phosphoinositol 3-kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR), and VEGFR pathways. These dose-dependent effects include inflammation of the pilo-sebaceous follicle (papulopustular rash, folliculitis), alteration in the skin barrier (photosensitivity, hyperpigmentation, xerosis, pruritus, skin fissures, radiation dermatitis) and lesions of the skin appendages (paronychia, facial hypertrichosis, trichomegaly, and so forth). Transgenic mice bearing the dominant negative mutant of EGFR demonstrated that the lack of EGFR activation was associated with interfollicular epidermal keratinocyte hyperplasia in conjunction with the necrosis and disappearance of the follicles, accompanied by strong infiltration by inflammatory cells characteristic of a foreign body reaction.[2] Histopathologic studies of patients' papulopustular rash reveal similar findings,[3] which provide a rationale for the general approach in the management of such epidermal side effects. Figure 3 shows a representative rash due to EGFR TKI therapy.

EGFR inhibitor-induced dermatologic toxicities are associated with worse quality of life (QoL) scores,[4,5] particularly in younger patients.[5] Of note, smoking status and lower skin phototype (ie, lighter skin pigmentation) have been inversely correlated with rash severity from EGFR tyrosine kinase inhibitors (TKI) whereas male sex and younger age are correlated with increased risk of rash from EGFR monoclonal antibodies (mAbs).[6–8] Use of sunscreen has been incorporated into various practice guidelines as one of the recommended preventive measures in the management of EGFR inhibitor-induced skin reactions.[8–10] Nonetheless, the 4-week regimen using sunscreen with SPF 60 neither reduced the incidence and severity of rash

TABLE 1. Summary of Selected Adverse Effects Reported in Registrational Studies of FDA-Approved Agents (and in Select Agents Pending FDA Review) and Their Corresponding Management

DRUG CLASS/TARGET	FREQUENCY		DRUGS	MANAGEMENT[a]
	AEs ALL GRADES	AEs GRADE 3+		
Dermatologic				
Rash				
EGFR inhibitors	49%-95%	5%-18%	Vandetanib < Erlotinib[b], Panitumumab < Cetuximab	Prophylactic treatment with oral minocycline or doxycline should be considered, in particular for EGFR/B-raf/MEK inhibitors. Apply broad-spectrum sunscreen. Avoid alcohol-containing skin products. Emollients and mild topical steroids (eg, 1% hydrocortisone cream) can be applied on dry skin 2x-3x daily. Topical antibiotics can be applied on papulopustular eruptions. For skin rash with moderate pruritus or tenderness, use 0.1% triamcinolone or 2.5% hydrocortisone cream. Withhold treatment for CTC ≥ grade 3 rash and start oral corticosteroids if rash remains severe despite intake of oral antibiotics. May resume when ≤ grade 1 at reduced dose. Continue prophylactic treatment. Avoid lansoprazole use with imatinib due to potential increased risk of dermatologic toxicity.
HER2 inhibitors	4%-44%	<1%-2%	Trastuzumab, Pertuzumab < Lapatinib	
B-raf inhibitors	36%-37%	0%-8%	Vemurafenib, Dabrafenib	
B-raf/MEK inhibitor combination	20%-27%	0%	Dabrafenib+Trametinib	
MEK inhibitor	84%-85%	4%-8%	Trametinib	
Multikinase angiogenesis inhibitors	8%-40%	<1%-6%	Axitinib, Cabozantinib, Pazopanib, Sunitinib <Regorafenib, Sorafenib,<Ponatinib	
mTOR inhibitors	22%-59%	<1%-5%	Everolimus, Temsirolimus	
ALK/c-met inhibitors	16%	0%	Crizotinib	
Multikinase Abl inhibitors	11%-49%	<1%-7%	Dasatinib < Imatinib < Nilotinib, Ponatinib, Bosutinib	
BTK inhibitors	16%-28%	0%	Ibrutinib	
HDAC inhibitors	4%-27%	<1%-8%	Romidepsin	
Proteasome inhibitors	18%-19%	1%	Bortezomib	
RXR agonist	17%-23%	2%-4%	Bexarotene (dose-dependent risk)	Withhold treatment for CTC > 2 grade or higher rash. Reduce dose by 100 mg/m^2/day upon resumption of treatment when CTC ≤ grade 1. Permanently discontinue for severe exfoliative/bullous rash or if Stevens-Johnson syndrome is suspected.
Immunomodulatory agents	21%-30%	4%	Thalidomide, Lenalidomide, Pomalidomide	Withhold treatment for CTC ≥ 2 grade or higher rash. May resume at 50% dose reduction upon resolution to baseline or less than grade 1 toxicity. Permanently discontinue for severe exfoliative/bullous rash or if Stevens-Johnson syndrome is suspected.
Anti-CTLA4 antibody	29%	2%	Ipilimumab	For moderate rash, withhold therapy and resume once dermatitis improves or becomes localized. Administer topical (eg, 2.5% hydrocortisone) or systemic corticosteroids if rash does not improve in a week or in the presence of ulcerative or bullous component. May resume therapy once prednisone dose is ≤7.5 mg/day or its equivalent. If symptoms worsen or if presenting with severe reaction (eg, Stevens Johnson syndrome, toxic epidermal necrolysis), permanently discontinue ipilimumab. Initiate prednisone 1-2 mg/kg/day or its equivalent. Steroid taper over a month maybe started once rash is improved.
Hand–foot skin reaction				
Multikinase angiogenesis inhibitors	6%-50%	2%-17%	Pazopanib < Axitinib ≤ Sunitinib < Sorafenib, Regorafenib, Cabozantinib	Preventive measures should be instituted early (callus removal, minimize friction and direct trauma by wearing well-fitted shoes, gloves, thick socks, well-padded footwear, gel-pad inserts). Application 2x-3x a day of moisturizers containing salicylic acid, urea or ammonium lactate recommended upon initiation of treatment. For painful blisters, topical corticosteroids should be considered. Interrupt treatment for painful or intolerable CTC grade 2 or higher toxicities. Dose reduction to be considered as clinically indicated upon resumption of treatment when toxicity improves to CTC grade <2.
Ligand-binding angiogenesis inhibitors	11%	3%	Aflibercept+FOLFIRI (higher incidence compared to chemotherapy only arm)	
EGFR inhibitors	19%	4%	Cetuximab+FOLFIRI (higher incidence compared to chemotherapy only arm)	
Cutaneous squamous cell cancer/keratoacanthoma				
B-raf inhibitors	19%-24%	17%-22%	Vemurafenib, Dabrafenib	Baseline skin examination and regular dermatologic evaluation. Local excision treatment as indicated.
B-raf/MEK inhibitor combination	2%-7%	2%-5%	Dabrafenib+Trametinib	

TABLE 1. (Continued)

DRUG CLASS/TARGET	FREQUENCY		DRUGS	MANAGEMENT[a]
	AEs ALL GRADES	AEs GRADE 3+		
Ocular				
EGFR inhibitors	4%-18%	0%-<1%	Corneal abnormalities, eg, kerato-conjunctivitis: Panitumumab < Erlotinib[a], Cetuximab, Vandetanib	Continue treatment. Consider the use of supportive measures (artificial tears, antibacterial ointment if superimposed infection is suspected). Ophthalmologic evaluation is recommended for patients with vision changes, persistent eye pain, photosensitivity or presence of other drug-induced ocular anomalies such as trichiasis. Withhold treatment for CTC grade 3 symptoms.
B-raf inhibitors	<1%-1.5%	NR	Uveitis, Retinal vein occlusion (RVO): Vemurafenib	Baseline and periodic ophthalmologic examination to be considered during MEK inhibitor therapy. Withhold treatment and coordinate ophthalmologic evaluation for CTC grade 2 or 3 visual changes. If no RVO or chorioretinopathy, may restart treatment at lower dose if symptoms promptly improve to ≤ grade 1. For prolonged recovery or grade 4 visual changes, permanently discontinue treatment. Chorioretinopathy is generally reversible upon drug discontinuation.
B-raf/MEK inhibitor combination	0-2%	2%	Chorioretinopathy: Dabrafenib+Trametinib	
MEK inhibitors	<1-1.5%	NR	Retinal vein occlusion, Chorioretinopathy: Trametinib	
ALK/c-met inhibitors	64%	0%	Vision disorders/light-dark adaptation: Crizotinib	Self-limiting. No dose interruption or reduction required.
Anti-CTLA4 antibody	<1%	NR	Uveitis, iritis, episcleritis: ipilimumab	Administer corticosteroid or immunosuppressive eye drops. Ophthalmologic examination recommended. Permanently discontinue for severe symptoms or if unresponsive to local therapies aforementioned. Initiated prednisone 1-2 mg/kg/day or its equivalent. May taper over a month once symptoms improved.
Cardiovascular				
Decreased left ventricular ejection fraction[LVEF]/congestive heart failure [CHF]				
Angiogenesis inhibitors (ligand-binding or multikinase inhibitors)	<1%-16%	<1%-7%	Bevacizumab, Aflibercept < Pazopanib, Sorafenib, Sunitinib, Vandetanib, Ponatinib	Before starting treatment, careful evaluation and treatment of risk factors (eg, uncontrolled hypertension, coronary artery disease, sleep disorders, smoking, diabetes mellitus, subclinical thyroid disorders, alcohol and other potential substance abuse) should be done. Close collaboration with cardiologist is recommended especially in high-risk patients. Baseline and periodic evaluation (eg, every 3 months) of LVEF is recommended for patients with known risk factors. If symptomatic, LVEF decline to < 50% or ≥ 10% from baseline, withhold treatment, institute heart failure medications and repeat LVEF measurement. May retreat if LVEF improves to 50% or <10% change from baseline. Discontinue treatment for CTC ≥ grade 3 heart failure, LVEF decline > 20% from baseline, recurrent LVEF decline upon rechallenge. A representative management algorithm can be found at jco.ascopubs.org/content/25/25/3859/F2.large.jpg
HER2 inhibitors	2%-7%	<1%-NR	Lapatinib< Trastuzumab, Pertuzumab	
Braf/MEK inhibitor combination	4%-9%/0%-2%	0%-2%/0%-2%	Dabrafenib + Trametinib	
MEK inhibitor	8%-10%	<1%-1%	Trametinib	
Multikinase Abl inhibitors	1%-7%	<1%-4%	Imatinib, Nilotinib, Bosutinib < Dasatinib, Ponatinib	
Hypertension				
Angiogenesis inhibitors (ligand-binding or multikinase inhibitors)	9%-67%	2%-19%	Sorafenib, Bevacizumab < Axitinib ≤ Sunitinib, Pazopanib, Regorafenib, Cabozantinib, Vandetanib ≤ Ponatinib < Aflibercept	BP should be controlled prior to initiating treatment. BP should be monitored early within the first week of treatment standard anti-hypertensive therapy should be initiated promptly, preferably with ACEi if there are no contraindications. Target BP is < 140/90 mm Hg. Treatment should be interrupted for severe hypertension (≥ 200 mm Hg or ≥110 mm Hg diastolic), hypertensive urgency or persistent hypertension despite anti-hypertensive medications. Dose reduction should be implemented upon improvement in BP control. Treatment should be permanently discontinued in patients with life-threatening symptoms (eg, reversible posterior leukoencephalopathy syndrome) or with persistently uncontrolled hypertension despite antihypertensive medications.
QT prolongation				
Multikinase angiogenesis inhibitors	NR-14%	<1%-8%	Cabozantinib, Ponatinib << Pazopanib, Sunitinib << Vandetanib (69% had QT prolongation > 450 ms and 7% had QT prolongation > 500 ms)	Use with caution in patients with pre-existing cardiac disease (eg, bradycardia, heart failure, on anti-arrhythmic) or concomitant medications that may prolong QT interval. Baseline and periodic monitoring of ECG as well as maintenance of adequate electrolyte balance are recommended. As these agents can cause diarrhea, associated electrolyte disturbances can elevate risk for toxicity.
ALK/c-met inhibitors	NR	1.3%-3.5%	Crizotinib (3.5% incidence of > 60 msec increase in QTc from baseline)	

TABLE 1. (Continued)

DRUG CLASS/TARGET	FREQUENCY		DRUGS	MANAGEMENT[a]
	AEs ALL GRADES	AEs GRADE 3+		
Multikinase Abl inhibitors	NR	4%	Ponatinib ≤ Bosutinib < Dasatinib < Nilotinib	Risk evaluation and mitigation strategy (REMS) program had been created for vandetanib and nilotinib. Vandetanib can be prescribed only through the REMS program. These agents should not be started in patients whose baseline QTcF is > 450 ms, in patients with congenital long QT syndrome, uncorrected hypokalemia or hypomagnesemia, history of torsades de pointes, uncompensated heart failure, bradyarrhythmias. Strict adherence to frequent monitoring of ECG and electrolyte balance is required. Nillotinib should be taken on fasting state (increased absorption and risk for QTc prolongation with food intake). Vandetanib exposure is increased in patients with impaired renal function and starting dose should thus be reduced to 200 mg daily if creatinine clearance is < 50 mLl/minute. Withhold treatment if QTc prolongs to ≥500 ms. May resume at reduced dosage if QTc < 450 ms.
HDAC inhibitors	4.3%	<1%-2%	Romidepsin, Vorinostat	
Venous thromboembolic events (VTE)				
Angiogenesis inhibitors (ligand-binding or multikinase inhibitors)	1%-14%	3%-9%	Bevacizumab, Sorafenib, Axitinib, pazopanib, Sunitinib, Ponatinib < Cabozantinib < Bevacizumab or Aflibercept in combination with chemotherapy(higher incidence compared to chemotherapy only arm)	Withhold treatment and initiate standard anticoagulant treatment; may resume at original dose following stabilization of patient, resolution of acute symptoms and achievement of therapeutic levels of anticoagulation. Maintain anticoagulant treatment for duration of therapy. Routine prophylactic anticoagulation is recommended in patients receiving combination regimens with immunomodulatory agents or in the presence of risk factors (eg, known inherited or acquired thrombophilia).
Immunomodulatory agents	9%-22%	8%-21%	Pomalidomide, Lenalidomide < Thalidomide	Prophylaxis with low-molecular weight heparin (equivalent to enoxaparin 40 mg once daily) or full-dose warfarin (INR target 2-3) should be considered in all patients who receive multiagent treatment regimen (e.g., in combination with high-dose dexamethasone or in combination with chemotherapy). Use of aspirin alone should be limited only to patients with ≤ 1 risk factor (risk factors are: > 65 years old, obesity, presence of central venous catheter, inherited thrombophilia, increased blood viscosity, comorbidities such as diabetes mellitus or cardiac disease).
Arterial thromboembolic events				
Angiogenesis inhibitors (ligand-binding or multikinase inhibitors)	1%-11%	1%-8%	Bevacizumab, Aflibercept, Axitinib, Sorafenib, Pazopanib, Sunitinib, Regorafenib, Cabozantinib, Vandetanib < Ponatinib	Treatment should be used with caution in patients at risk for these complications and avoided in patients with recent events in the preceding 6-12 months. Withhold treatment upon occurrence of adverse effect and consider permanent discontinuation for treatment-related life-threatening manifestations. If resumption of therapy is strongly indicated, may resume at original dose following stabilization of patient, resolution of acute symptoms and achievement of therapeutic levels of anticoagulation.
Multikinase Abl inhibitors	<1%-11%	<1%-8%	Imatinib < Nilotinib, Bosutinib < Dasatinib << Ponatinib	
Respiratory				
Noninfectious pneumonitis/diffuse alveolar damage/pulmonary fibrosis				
Multikinase angiogenesis inhibitors	NR	<1%	Sorafenib, Sunitinib	No dose adjustment necessary in patients who are asymptomatic or who have mild symptoms associated with radiological changes suggesting interstitial pneumonitis. Follow-up with high-resolution CT scan every 6-8 weeks. Consider either treatment interruption or dose reduction along with corticosteroid initiation (0.75-1 mg/kg/day prednisone or its equivalent) for moderate symptoms once infectious, neoplastic and other etiology have been excluded. Withhold treatment for rapidly developing symptoms, worsening symptoms despite dose reduction on corticosteroids or with severe symptoms upon initial presentation. Consider hospitalization and perform bronchoscopy with lavage studies. Initiate high-dose corticosteroids (at least 2 mg/kg/day prednisone or its equivalent). Continue corticosteroids at the same dose until symptom improvement is obtained before starting taper.
mTOR inhibitors	14%-45%	2-4%%	Everolimus, Temsirolimus	
EGFR inhibitors	NR	<1%	Erlotinib[a], Cetuximab, Panitumumab	
HER2 inhibitors	NR	<1%	Trastuzumab	
ALK/c-met inhibitor	NR	1.6%	Crizotinib	
Multikinase Abl inhibitors	NR	<1.5%	Dasatinib, Imatinib	
Proteasome inhibitors	NR	<1%	Bortezomib, Carfilzomib	
Immunomodulatory agents	NR	<1.5%	Thalidomide, Lenalidomide	

TABLE 1. (Continued)

DRUG CLASS/TARGET	FREQUENCY		DRUGS	MANAGEMENT[a]
	AEs ALL GRADES	AEs GRADE 3+		
				Risk maybe elevated 5- to 20- fold higher in Asia than in other countries. Switching therapy to a different agent in the same drug class has documented success in case reports (eg, nilotinib in imatinib-induced interstitial lung disease, erlotinib after gefitinib-induced interstitial lung disease). In patients receiving mTOR inhibitors, treatment with the same agent maybe reintroduced at 50% reduction upon improvement in symptoms to ≤ CTC grade 1. Successful rechallenge with the same agent for corticosteroid-responsive pneumonitis had also been described for erlotinib and imatinib. Permanently discontinue treatment in patients with life-threatening pneumonitis. A representative management algorithm for inhibitors of PI3K/mTOR/AKT pathway can be found at annonc.oxfordjournals.org/content/23/8/1943/F2.large.jpg
Anti-CTLA4 antibody	NR	<1%	Ipilimumab	Continue treatment if patients are asymptomatic in the presence of radiologic changes suggestive of interstitial pneumonitis. Upon exclusion of neoplastic or infectious etiology, administer short course of corticosteroids in patients with mild symptoms and corroborating radiologic findings. Withhold treatment for moderate to severe symptoms or if symptoms do not improvement within a week of corticosteroid therapy. May resume treatment if symptoms are controlled with prednisone dose ≤ 7.5 mg/day prednisone or its equivalent. Initiate systemic corticosteroids at a dose of 1-2 mg/kg/day prednisone or its equivalent for moderate to severe pneumonitis. May begin slow taper over at least 4 weeks upon clinically relevant improvement of symptoms (ie, minimal effect on instrumental activities of daily living). Permanently discontinue in patients with life-threatening complications.
Pulmonary arterial hypertension				
Multikinase Abl inhibitors	1%	0%	Dasatinib	Periodic assessment of pulmonary arterial pressure or upon development of suggestive symptoms (dyspnea, cough, fluid retention). Withhold therapy if CTC grade 2 or higher. Treatment may be resumed upon improvement as clinically indicated. Permanently discontinue for CTC grade 3 or higher manifestations.
Proteasome inhibitor	2%	<1%	Carfilzomib	
Gastrointestinal				
Mucositis/stomatitis				
Angiogenesis inhibitors (ligand-binding or multikinase inhibitors)	7%-50%	1%-13%	Cabozantinib, Ponatinib, Sorafenib, Pazopanib, Axitinib << Regorafenib ≤ Sunitinib ≤ Bevacizumab or Aflibercept in combination with 5FU-based chemotherapy (higher incidence compared to chemotherapy-only arm)	Avoid alcohol- or peroxide-based mouthwashes. Antifungal agents should be used if infection is confirmed. Anesthetic mouthwashes (typically containing equal parts of lidocaine, diphenhydramine or dimethicone and magnesium hydroxide) may provide brief symptomatic relief if mild. Institute topical dexamethasone rinses (0.1 mg/mLl) or topical corticosteroids. Persistent CTC grade 2 symptoms or worsening symptoms require withholding treatment and intralesional corticosteroid therapy for severe mucositis. Initiate systemic corticosteroids (prednisone 1 mg/kg or its equivalent) if inadequate relief with intralesional therapy or for CTC ≥ grade 3 presentation. Treatment may be resumed with dose reduction upon symptom improvement to CTC ≤ grade 1. Consider permanent discontinuation of treatment in patients with life-threatening presentations (eg, concomitant esophagitis, diarrhea, or vaginal ulcers suggestive of widespread involvement).
mTOR inhibitors	41%-78%	3%-8%	Temsirolimus, Everolimus	
EGFR inhibitors	7%-32%	<1%-3%	Panitumumab < Erlotinib[a] < Cetuximab	
HER2 inhibitors	14%-28%	0%-1.5%	Lapatinib < Trastuzumab, Pertuzumab	
Multikinase Abl inhibitors	5%-7%	<1%-1%	Imatinib < Ponatinib	

TABLE 1. (Continued)

DRUG CLASS/TARGET	FREQUENCY		DRUGS	MANAGEMENT[a]
	AEs ALL GRADES	AEs GRADE 3+		
Diarrhea/colitis				
Angiogenesis inhibitors (ligand-binding or multikinase inhibitors)	18%-66%	<1%-34%	Bevacizumab, Ponatinib < Sorafenib, Axitinib, Pazopanib, Regorafenib, Sunitinib, Vandetanib, Cabozantinib, Bevacizumab or Aflibercept in combination with chemotherapy	While investigating the cause of diarrhea, anti-motility agents (eg, loperamide, diphenoxylate/atropine) should be initiated upon appearance of mild symptoms, particularly in patients receiving combination with chemotherapy agents known for causing diarrhea and in patients receiving EGFR/-RAF/-MEK pathway inhibitors. Withhold treatment for persistent CTC grade 2 symptoms despite use of anti-motility agents and resume upon improvement to baseline or CTC grade 1. May consider adding octreotide. Withhold treatment for CTC ≥ grade 3 diarrhea and resume at a lower dose upon improvement to baseline or CTC grade 1.
EGFR inhibitors	20%-66%	2% - 16%	Panitumumab < Cetuximab < Erlotinib[a], Vandetanib	
HER2 inhibitors	7%- 67%	<1%-14%	Trastuzumab, Pertuzumab < Lapatinib, Trastuzumab or Pertuzumab in combination with chemotherapy	
B-raf inhibitors	28%	<1%	Vemurafenib	
B-raf/MEK inhibitor combination	26%-36%	0%-2%	Dabrafenib+Trametinib	
MEK inhibitor	42%-46%	<1%-1%	Trametinib	
BTK inhibitor	43%-54%	4%	Ibrutinib	
Multikinase Abl inhibitors	14%-82%	<1%-8%	Nilotinib, Ponatinib, Dasatinib, Imatinib, < Bosutinib	
Anti-CTLA4 antibody	8%-32%	5%	Ipilimumab	Administer antimotility agents if infectious etiology excluded. Withhold therapy for moderate symptoms. May resume treatment if symptoms improved. If symptoms persistent > 5-7 days despite use of antimotility agents, withhold therapy and start systemic corticosteroids (eg, 0.5 mg/kg/day of prednisone or its equivalent) and may resume treatment if symptoms controlled at prednisone ≤ 7.5 mg/day. If symptoms worsen, severe at the onset or persistent grade 2 diarrhea despite oral corticosteroids, permanently discontinue ipilimumab and administer 1-2 mg/kg/day of prednisone or its equivalent. Must taper slowly over a month to avoid recrudescence once symptoms improved. Endoscopic evaluation recommended. May consider other immunosuppressants such as infliximab for refractory cases or relapsing diarrhea upon steroid reduction.
Dysgeusia				
SMO receptor inhibitors	55%	NR	Vismodegib	Consider dietary and food preparation counseling. The efficacy of food additives that enhance or change taste perception, eg, marmite, miraculin, nori, mosodium glutamate, is unproven.
Musculoskeletal				
Muscle spasms/cramps/myalgia				
SMO receptor inhibitors	72%	4%	Vismodegib	Empiric supportive treatment should be instituted (eg, maintenance of adequate fluid and electrolyte intake, anti-inflammatory and analgesic medications). Withhold treatment for CTC grade 3 symptoms. May resume at lower dose upon improvement to ≤ grade 1.
Neurologic				
Neuropathy				
Immunomodulatory agents	6.5%-54%	4%	Pomalidomide, Lenalidomide << Thalidomide	Continue treatment but consider dose reduction if CTC grade 1 symptoms develop. Withhold treatment for patients CTC ≥ grade 2 symptoms. Institute empiric supportive medications as appropriate. Upon improvement to CTC <grade 1, may resume treatment at 50% dose reduction. Consider using lower dose for chronic maintenance regimen. If recurrent using lower dose or if CTC grade 3 or higher, discontinue treatment. Administer 1-2 mg/kg/day of prednisone or its. IV immunoglobulin or other immmunosuppressants may be considered.

TABLE 1. (Continued)

DRUG CLASS/TARGET	FREQUENCY		DRUGS	MANAGEMENT[a]
	AEs ALL GRADES	AEs GRADE 3+		
Proteasome inhibitors	14%-47%	<8%-14%	Carfilzomib << Bortezomib	Consider dose reduction for mild pain symptoms or if affecting function. Institute empiric supportive medications as appropriate. Withhold treatment for moderate pain or symptoms affect activities of daily living. Upon improvement, institute dose reduction. Consider alternate schedule (weekly) and route of administration (subcutaneous). If CTC grade 3 or higher, discontinue treatment.
Anti-CTLA4 antibody	1%	1%	Ipilimumab	Withhold therapy for moderate symptoms and institute empiric supportive medications as appropriate. May resume upon improvement to baseline or if CTC grade 1. Permanently discontinue ipilimumab in patients with CTC grade 3 manifestations. Administer 1-2 mg/kg/day of prednisone or its equivalent.
Endocrine/Metabolic				
Hypothyroidism				
Multikinase angiogenesis inhibitors	4%-57%	<1%-2%	Sorafenib, Pazopanib, Regorafenib, Axitinib, Sunitinib < Vandetanib, Cabozantinib	Monitor TSH and free T4 at baseline, every 2-3 months and upon development of relevant symptoms. Institute hormone replacement as indicated.
Immunomodulatory agents	5%-20%	7%	Lenalidomide < Thalidomide	
RXR agonist	29%-53%	2%-4%	Bexarotene (dose-dependent risk)	Levothyroxine supplementation at 25-50 ug/day should be initiated concomitantly. Monitor both TSH (indication of bexarotene compliance) and free T4 levels every 1-2 months. As bexarotene may result in increased T4 metabolism, replacement doses may be as high as 200-250 ug/day.
Hypogonadism/hypopituitarism				
Anti-CTLA4 antibody	4%	<2%	Ipilimumab	Monitor symptoms, thyroid hormone and electrolyte levels frequently. For patients requiring hormone replacement or with severe symptoms, withhold treatment and administer 1-2 mg/kg/day of prednisone or its equivalent. May resume ipilimumab once hormone replacement dose is stable and symptoms controlled at prednisone 7.5 mg/day.
c-met/ALK inhibitors	NR	NR	Hypogonadism (case series reported 80-100% incidence): Crizotinib	Monitor symptoms (erectile dysfunction, fatigue, loss of muscle mass, etc.) and check testosterone level with consideration of testosterone replacement therapy as indicated.
Hypercholesterolemia				
mTOR inhibitors	70%-87%	<1%-4%	Everolimus, Temsirolimus	No dosage adjustment for CTC grade 1 or 2 changes. Institute appropriate lifestyle (exercise, diet, limiting alcohol consumption) and pharmacologic interventions. Withhold treatment for CTC grade 3 toxicity. Reinitiate at a lower dose when baseline or CTC grade 2.
RXR agonist	32%-62%	25%-45%	Bexarotene (dose-dependent risk)	
JAK inhibitors	17%	0%	Ruxolitinib	
Hypertriglyceridemia				
mTOR inhibitors	50%-83%	<1%-44%	Everolimus, Temsirolimus	No dosage adjustment for CTC grade 1 or 2 changes. Institute appropriate lifestyle (exercise, diet, limiting alcohol consumption, avoid grapefruit) and pharmacologic interventions. Correct concomitant hypothyroidism. Aim for levels < 500 mg/dl (or < 300 mg/dl in patients with cardiovascular risk factors). Reduce dose if > 650 mg/dl (or > 500 mg/dl) despite receiving maximal antihyperlipidemic treatment. Withhold treatment if > 800 mg/dl due to risk of pancreatitis.
RXR agonist	79%	28%-45%	Bexarotene (dose-dependent risk)	Fenofibrate or rosuvastatin should be initiated regardless of baseline lipid profile, one week prior to commencing treatment. Gemfibrozil is contraindicated as it results in higher plasma levels of bexarotene and an elevation of triglycerides. Increase monitoring with the use of

TABLE 1. (Continued)

DRUG CLASS/TARGET	FREQUENCY		DRUGS	MANAGEMENT[a]
	AEs ALL GRADES	AEs GRADE 3+		
				alternative HMG-CoA reductase inhibitors metabolized by CYP3A4 (eg, decreased plasma levels of atorvastatin). Aim for levels < 500 mg/dL (or <300 mg/dL in patients with cardiovascular risk factors). Correct concomitant hypothyroidism. Reduce dose if > 650 mg/dL (or >500 mg/dL) despite receiving maximal antihyperlipidemic treatment. Withhold treatment if >800 mg/dL due to risk of pancreatitis.
Hyperglycemia				
mTOR inhibitors	14%-89%	0%-16%	Everolimus, Temsirolimus	Monitor fasting blood sugar and hemoglobin A1c closely. No dosage adjustment for CTC grade 1 or 2 changes. Institute lifestyle changes (modification of dietary and exercise regimen). Start or adjust anti-diabetic medications per standard clinical practice. Withhold treatment for CTC grade 3 toxicity. Resume at a lower dose upon improvement to ≤ grade 2. Consider permanent discontinuation for grade 4 event.
Multikinase Abl inhibitors	NR-58%	0-6%	Nilotinib, Ponatinib	
Hypoglycemia				
Multikinase angiogenesis inhibitors	11%-24%	0%-2%	Axitinib, Sorafenib < Pazopanib, Sunitinib, Vandetanib, Ponatinib	Fasting blood sugar levels of patients on antidiabetic medications should be closely monitored. Dose reduction or discontinuation of antidiabetic medications may be required. No dosage adjustment for CTC grade 1 or 2 changes. Withhold treatment for CTC grade 3 or symptomatic CTC grade 2 toxicity and discontinue antidiabetic medications. Resume at the same dose when fasting glucose ≤ grade 1. For recurrent toxicity or if toxicity occurred in the absence of antidiabetic medications, reinitiate at a lower dose when fasting glucose < grade 1. Discontinue for persistent CTC grade 3 or symptomatic CTC grade 2 toxicity.
Multikinase Abl inhibitors	24%-47%	0%-<1%	Imatinib, Dasatinib, Ponatinib	
RXR agonist	NR	NR	Bexarotene	Preclinical murine model suggests the potential to enhance the activity of insulin. Fasting blood sugar levels of patients on insulin should be closely monitored and insulin dose adjusted as necessary.
Infections				
Herpes Zoster				
JAK inhibitors	1.9%	0%	Ruxolitinib	Routine antiviral prophylaxis should be considered, particularly in high-risk patients (eg, elderly, lack of age-appropriate HZV vaccination, chemotherapy or steroid combinations, etc.)
Proteasome inhibitors	2%-13%	2%	Carfilzomib (antiviral prophylaxis permitted in registrational study) < Bortezomib	
Constitutional				
Pyrexia				
B-raf inhibitors	19%-28%	0%-2%	Regorafenib, Vemurafenib, Dabrafenib	Typically self-limited but clinical evaluation should be performed to exclude sepsis. Conservative measures (fluid hydration, anti-pyretic medications, NSAIDs and narcotics for presence of accompanying moderate chills) generally adequate instituted promptly and early. Withhold treatment for CTC ≥ grade 3 reaction. Consider systemic steroids and hospitalization. May restart therapy at the same dose if ≤ grade 1. If recurrent CTC grade 3 or intolerable grade 2, consider low-dose systemic steroids upon resumption of treatment.
B-raf/MEK inhibitor combination	69%-71%	5%-9%	Dabrafenib + Trametinib	
BTK inhibitors	21%	2%	Ibrutinib	
Proteasome inhibitors	35%-35%	<4%	Bortezomib, Carfilzomib	
Hematologic				
Neutropenia				
Angiogenesis inhibitors (ligand-binding or multikinase inhibitors)	3%-77%	1%-37%	Bevacizumab ≤ Regorafenib, Sorafenib, Axitinib, Vandetanib < Pazopanib, Cabozantinib << Ponatinib, Sunitinib, Bevacizumab or Aflibercept in combination with chemotherapy	Withhold for ANC < 500 x 10^6/L until ANC 1000 x 10^6/L and platelets ≥ 50,000 x 10^6/L. Resume treatment at same dose in general if recovery occurs within 1-2 weeks. Risk of toxicity with vandetanib, lenalidomide, ruxolitinib is increased in patients with impaired renal function.

TABLE 1. (Continued)

DRUG CLASS/TARGET	FREQUENCY		DRUGS	MANAGEMENT[a]
	AEs ALL GRADES	AEs GRADE 3+		
			(higher incidence compared to chemotherapy only arm)	
mTOR inhibitors	14%-31%	<1%-5%	Everolimus, Temsirolimus	For lenalidomide and pomalidomide, dose reduction is implemented upon resumption of treatment if cytopenia occurs within the first 4 weeks of initial therapy. For prolonged cytopenia, reduce dose upon count recovery. If cytopenia recurs, further reduce dose. Refer to specific product labeling instructions for lenalidomide, pomalidomide, and ruxolitinib.
Multikinase Abl inhibitors	16%-> 36%	3%-36%	Imatinib, Nilotinib, Bosutinib, Dasatinib < Ponatinib	
BTK inhibitor	NR	12.5%	Ibrutinib	
JAK inhibitors	19%	7%	Ruxolitinib	
HDAC inhibitors	11%-66%	4%-47%	Romidepsin, Vorinostat	
RXR agonist	17%-47%	16%-26%	Bexarotene (dose-dependent effect)	
Immunomodulatory agents	31%-42%	10%-33%	Thalidomide < Lenalidomide, Pomalidomide	
Thrombocytopenia				
Angiogenesis inhibitors (ligand-binding or multikinase inhibitors)	5%-68%	<1%-42%	Bevacizumab Sorafenib, Axitinib, Vandetanib < Regorafenib, Pazopanib, Cabozantinib << Ponatinib, Sunitinib, Bevacizumab or Aflibercept in combination with chemotherapy (higher incidence compared to chemotherapy-only arm)	Withhold until ANC > 1000 x 10^6/L and platelets > 50,000 x 10^6/L. Resume treatment at same dose in general if recovery occurs within 1-2 weeks. Risk of toxicity with vandetanib, lenalidomide, ruxolitinib is increased in patients with impaired renal function.
mTOR inhibitors	19%-54%	0%-3%	Everolimus, Temsirolimus	For lenalidomide, dose reduction is implemented upon resumption of treatment if cytopenia occurs within the first 4 weeks of initial therapy. For prolonged cytopenia, reduce dose upon count recovery. If cytopenia recurs, further reduce dose. Refer to specific product labeling for platelet count-based dosing of ruxolitinib.
Multikinase Abl inhibitors	5%->42%	<1%-42%	Imatinib, Nilotinib, Bosutinib, Dasatinib < Ponatinib	
BTK inhibitor	NR	7%	Ibrutinib	
JAK inhibitors	70%	5%	Ruxolitinib	
HDAC inhibitors	17%-72%	0%-36%	Romidepsin, Vorinostat	
Immunomodulatory agents	22%-24%	4%-12%	Thalidomide < Lenalidomide, Pomalidomide	
Proteasome inhibitors	35%-52%	23%-37%	Bortezomib, Carfilzomib < Combination with chemotherapy	
Laboratory Investigations				
Transaminase elevations				
Angiogenesis inhibitors (ligand-binding or multikinase inhibitors)	20%-86%	<1%-12%	Axitinib, Sorafenib ≤ Sunitinib, Regorafenib, Aflibercept with FOLFIRI (higher incidence compared to chemotherapy only arm), Vandetanib, Ponatinib < Pazopanib ≤ Cabozantinib	Monitor liver tests at baseline and at least once monthly. Withhold treatment if AST or ALT levels if >5× ULN. If benefit of retreatment outweighs risk of hepatotoxicity, may resume treatment at reduced dose upon improvement in levels <3× ULN. Review concomitant medications (eg, known interaction of simvastatin with pazopanib in worsening hepatotoxicity) Refer to specific product labeling for dosing guidelines on pazopanib.
mTOR inhibitors	20%-56%%	1%-4%	Everolimus, Temsirolimus	
RXR agonists	NR	1%-4%	Bexarotene (dose-dependent risk)	
EGFR inhibitors	38%-43%	1-2%	Erlotinib[a], Cetuximab	
HER2 inhibitors	37%-53%	2-6%	Lapatinib (in combination with capecitabine or letrozole)	
B-raf inhibitors	NR	0.9%-2.8%	Vemurafenib	
ALK/c-met inhibitors	11%-15%	3%-7%	Crizotinib	
Multikinase Abl inhibitors	12%-53%	1%-9%	Dasatinib, Imatinib, Nilotinib, Bosutinib < Ponatinib	

TABLE 1. (Continued)

DRUG CLASS/TARGET	FREQUENCY		DRUGS	MANAGEMENT[a]
	AEs ALL GRADES	AEs GRADE 3+		
JAK inhibitors	18%-27%	0%-1.3%	Ruxolitinib	
Proteasome inhibitors	13%	3%	Bortezomib < Carfilzomib	
Anti-CTLA4 antibody	<5%	2%	Ipilimumab	Monitor levels and withhold therapy for levels > 2.5× ULN not due to infection or metastases. May resume treatment if level returns to baseline or ≤ 2.5× ULN. Administer 1-2 mg/kg/day of prednisone or its equivalent for >5× ULN. Permanent discontinuation should be considered. Steroid taper maybe initiated over a month once levels show pattern of sustained improvement. If resumption of treatment is clinically warranted, maintain prednisone treatment to keep ALT ≤ 2.5× ULN. Use of other immunosuppressants (eg, mycophenolate, tacrolimus, antithymocyte globulin) may be considered in severe or refractory cases.
Hyperbilirubinemia				
Multikinase angiogenesis inhibitors	13%-45%	0%-13%	Vandetanib < Axitinib, Sorafenib, Ponatinib, Cabozantinib ≤ Sunitinib < Regorafenib, Pazopanib	Withhold treatment for total bilirubin level >3x ULN (for patients with Gilbert's syndrome and elevated baseline total bilirubin level, may consider continuation of treatment until >1.5× to 2x baseline level whereupon treatment should be interrupted).
Hyperlipasemia				
Multikinase angiogenesis inhibitors	25%-56%	5%-18%	Axitinib, Pazopanib < Sorafenib, Regorafenib, Ponatinib, Sunitinib	Withhold treatment for patients with asymptomatic elevation in the presence of radiologic findings suggestive of pancreatitis. Resume at dose reduction upon recovery to ≤ grade 1. Withhold treatment for any degree of lipase elevations if symptomatic pancreatitis is suspected. Resume at dose reduction upon resolution of symptoms and recovery of lipase to ≤ grade 1.
Multikinase Abl inhibitors	NR-41%	3%-15%	Imatinib < Nilotinib, Bosutinib < Ponatinib	
Hypophosphatemia				
Angiogenesis inhibitors (ligand-binding or multikinase inhibitors)	13%-57%	2%-32%	Axitinib, Vandetanib < Pazopanib, Cabozantinib, Sunitinib < Sorafenib, Regorafenib, Ponatinib	Monitor serum calcium, vitamin D levels and bone mineral density. Correct deficient states with necessary supplementation.
mTOR inhibitors	37%-49%	6%-18%	Everolimus, Temsirolimus	
Multikinase Abl inhibitors	NR-57%	5%-8%	Nilotinib, Dasatinib, < Imatinib, Bosutinib, Ponatinib	
Hypomagnesemia				
EGFR inhibitors	11%-38%	4%-5%	Panitumumab, Cetuximab	Optimize management of diarrhea. Limit the use of medications with significant QT-prolongation potential. Oral supplementation maybe attempted though this is generally ineffective and poorly tolerated due to diarrhea. Weekly IV magnesium replacement maybe administered for patients with asymptomatic CTC grade 2 hypomagnesemia. For patients with CTC grade 3/4 or symptomatic hypomagnesemia, interrupt treatment. Replacement of magnesium intravenously every 2-3 days may be necessary. My resume treatment at the same dose once CTC grade ≤ 1 sustained without IV replacement.
Multikinase angiogenesis inhibitors	19%	1%	Cabozantinib	

ACEi indicates angiotensin-converting enzyme inhibitors; AE, adverse effect; BP, blood pressure; CTC, common toxicity criteria; LVEF, left ventricular ejection fraction; ULN, upper limit of normal.

[a]Proposed are general management approaches. Refer to each individual product label for more specific guidelines.

[b]Data for erlotinib applicable to gefitinib as well.

[c]Data in part from retrospective series for hypoglycemia from multikinase abl inhibitors.

nor improved the QoL scores compared to a placebo formulation in a small cohort of patients receiving an EGFR inhibitor.[4] Other negative prophylactic treatment trials include tazarotene and topical pimecrolimus.[11,12] In contrast, the administration of tetracycline antibiotics (tetracycline, minocycline, doxycline, lymecycline) as preventive

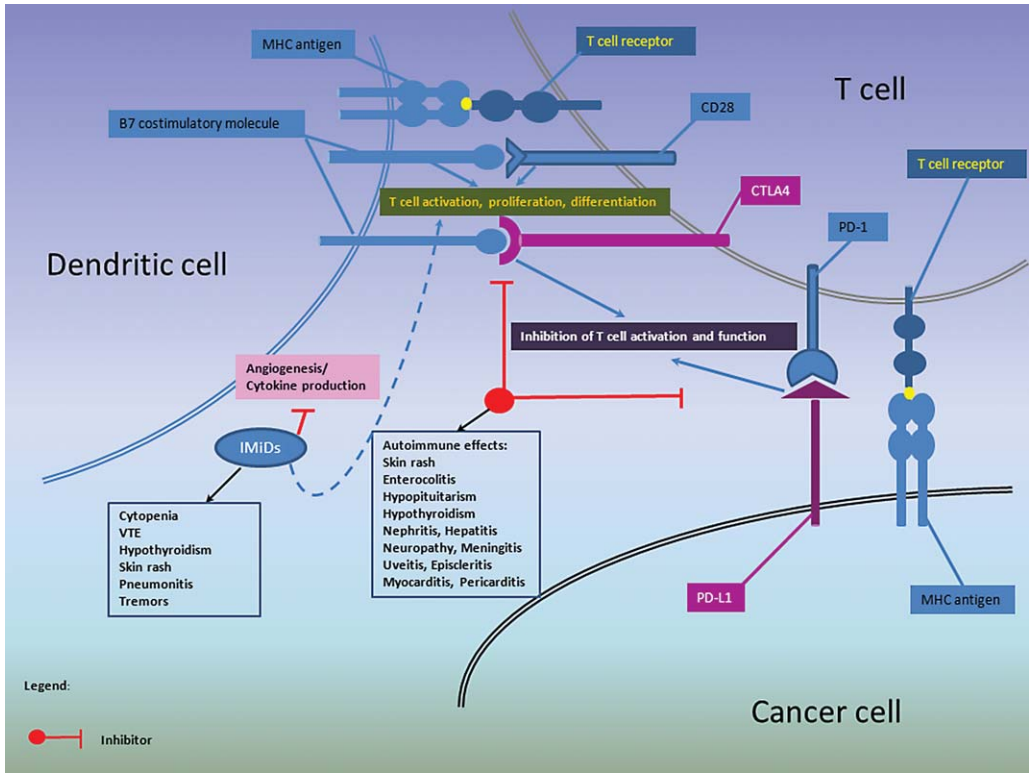

FIGURE 2. Toxicities Associated With Drugs Modulating the Immunologic Response. CTLA4 indicates cytotoxic T-lymphocyte antigen 4; IMiDs, thalidomide and its analogues; MHC, major histocompatibility complex; PD-1, programmed death 1; PD-L1, programmed death ligand.

therapy was associated with reduced severity of the papulopustular rash/folliculitis as well as improved QoL.[13] This may be attributed to nonantibiotic actions, such as immunomodulation and anti-inflammatory effects.[14] Their use in the prophylactic setting is currently recommended by various expert consensus statements.[8,9,13,15] On the other hand, when it comes to the treatment of dermatologic toxicities, there are no randomized studies supporting the use of tetracyclines or of topical corticosteroids. However, their known anti-inflammatory properties and the cumulative clinical experience to date make them the standard therapeutic agents of choice for cutaneous toxicity from targeted agents.[8,9,13,15] These approaches are generally used for rashes that occur in patients receiving other kinase inhibitors such as BRAF and MEK inhibitors. Table 2 lists a summary of expert recommendations in the management of other dermatologic toxicities.

Aside from the cutaneous toxicities described above, hyperkeratosis, development of both benign and malignant epithelial tumors such as keratoacanthomas and cutaneous squamous cell carcinomas (cSCC) are observed at higher frequencies among patients receiving agents that target RAF kinase, such as sorafenib (6% to 7% incidence of cSCC and/or keratoacanthomas).[16] These effects are particularly severe and more common with the selective BRAF V600E inhibitors such as vemurafenib (24%) and dabrafenib (6%).[17-19] The median time to onset of cSCC is approximately 2 months.[18,20] This phenomenon has been attributed to the paradoxical activation of MAPK signaling by transactivation of CRAF as it heterodimerizes with the inhibitor-bound BRAF,[21,22] and appears to be facilitated by the presence of mutant RAS. The development of cSCC has been suppressed by combination with an inhibitor of MEK, which is downstream to RAF signaling.[23,24] Due to the low risk of metastasis from these hyperproliferative lesions, the potential for spontaneous regression and the ease of definitive management (eg, surgical resection or local ablative approaches such as cryotherapy, photodynamic therapy or electrodessication), this toxicity does not require the discontinuation of the BRAF inhibitor. Use of

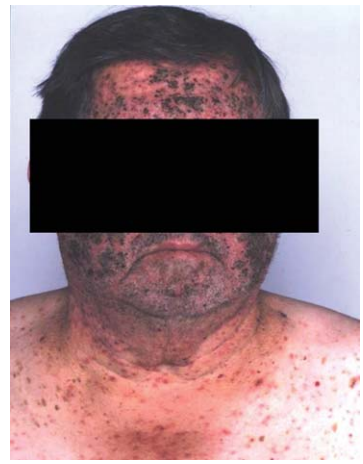

FIGURE 3. A Typical Rash Associated With EGFR TK Inhibitors.

TABLE 2. Summary of Treatment Recommendations for Other Dermatologic Toxicities

TOXICITY	INTERVENTION[a]
Radiation dermatitis	Topical corticosteroids
	Nonalcoholic drying solutions for exudative lesions
	Antibiotics when infection is suspected
	Not recommended: pentoxifylline or trolamine emulsion as prophylaxis
Xerosis	Hypoallergenic moisturizing emollients or creams
	Avoid topical retinoids or other preparations that dry skin (eg, alcohol- or peroxide-gels)
	Avoid hot water baths/excessive bathing
Pruritus	Oral antihistamines
	Topical agents such as antihistamines, calamine, and menthol should not be used routinely due to limited data/mixed results
	Limited data on antiepileptic agents in refractory cases
Paronychia	Oral tetracycline agents
	Topical corticosteroids
	Antimicrobial soaks
	Local care (minimize trauma by avoiding tight shoes, avoid overzealous manicure/pedicure)
Fissures	Avoiding friction to skin to prevent fissures
	Liquid glue to seal cracks may help pain relief and prevent infection
	Steroid tape and hydrocolloid dressings for erythematous areas

[a]In general, temporary drug discontinuation is recommended while instituting interventions to manage skin reactions grade ≥ 3.

systemic retinoids, such as bexarotene, has been reported to be an effective therapy as an alternative to surgery when there are multiple and/or unresectable lesions.[25] In comparison, there are no cSCC or other hyperproliferative skin disorders with MEK inhibitors.[26-28] Early results from the study combining dabrafenib with trametinib, a MEK inhibitor, suggest a lower incidence of MEK inhibitor–related rash as well as BRAF inhibitor–associated cSCC (2%) compared with either agent alone.[29]

Other exanthematous drug reactions, ranging from maculopapular eruptions to Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported with virtually all novel drug classes. Some of the milder exanthemata are self-limited and transient. The more severe and extensive rashes are generally reversible upon treatment discontinuation. Anecdotally, in early reports of patients receiving vemurafenib, severe drug hypersensitivity reactions manifesting as maculopapular rash within a week of treatment were associated with prior exposure to ipilimumab.[30]

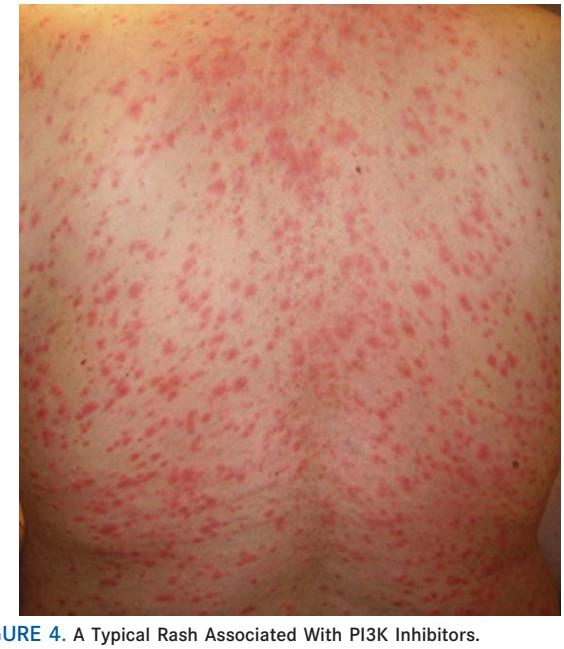

FIGURE 4. A Typical Rash Associated With PI3K Inhibitors.

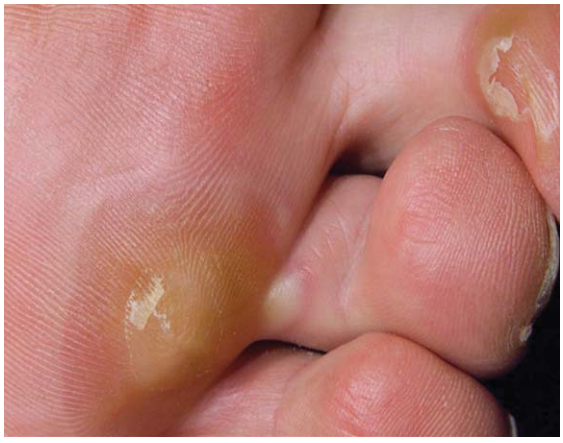

FIGURE 5. A Typical Hand–Foot Skin Reaction Associated With Multikinase Inhibitors.

TABLE 3. Drug Transport, Metabolism, and Other Interactions of Selected FDA-Approved Targeted Agents in Oncology

DRUG	CYP3A4 SUBSTRATE[a]	CYP 3A4 INHIBITOR/INDUCER[a]	P-GLYCOPROTEIN SUBSTRATE/INHIBITOR[b]	ADMINISTRATION (FOOD EFFECT)	WARFARIN PK/INR PROLONGATION
Axitinib	Yes	No	Inhibitor[c]	No effect	Unlikely/unknown
Cabozantinib	Yes	Weak inhibitor	Inhibitor	Fasting (increased Cmax and AUC with high-fat meal)	Enhanced (potential)
Pazopanib	Yes	Weak inhibitor	Substrate	Fasting (increased AUC and Cmax with food and crushing tablets)	Enhanced (potential)
Regorafenib	Yes	Weak inhibitor	Inhibitor	Administer with low-fat meal	Enhanced (potential)
Sorafenib	Yes[d]	Weak inhibitor[c]	Inhibitor	Fasting (reduced bioavailability with high-fat meal)	None
Sunitinib	Yes	No	Inhibitor	No effect	None
Vandetanib	Yes[d]	No	Inhibitor	No effect	Unlikely/Unknown
Everolimus	Yes	Weak inhibitor[c]	Substrate/Inhibitor	With or without food (no significant effect)	Unlikely/Unknown
Temsirolimus	Yes	Weak inhibitor[c]	Substrate/Inhibitor	IV (NA)	Unlikely/Unknown
Erlotinib	Yes	No	Substrate/Inhibitor	Fasting (increased AUC and Cmax with food)	Enhanced
Lapatinib	Yes	Weak inhibitor	Substrate/Inhibitor	Fasting (increased AUC and Cmax with food)	Enhanced (potential)
Vemurafenib	Yes	Weak inducer	Substrate/Inhibitor	With or without food (unknown)	Enhanced
Bosutinib	Yes	No	Substrate/Inhibitor	Administer with food (increased AUC and Cmax with high fat meal)	Unlikely/Unknown
Dasatinib	Yes	Weak inhibitor	Substrate/Inhibitor	No effect	Enhanced (potential)
Imatinib	Yes	Moderate inhibitor	Substrate/Inhibitor	Administer with food (unknown)	Enhanced (potential)
Nilotinib	Yes	No	Substrate/Inhibitor	Fasting (increased AUC with high-fat meal)	No effect
Ponatinib	Yes	No	Inhibitor	No effect	Unlikely/Unknown
Vismodegib	Negligible	No	Substrate	No effect	Enhanced (potential)
Romidepsin	Yes	No	Substrate	IV (NA)	Enhanced
Vorinostat	Negligible	No	Neither	Administer with food (high-fat meal increases AUC)	Enhanced
Bexarotene	Yes[d]	Weak/moderate inducer	-	Administer with food (higher AUC and Cmax with fat compared to glucose)	Reduced (potential)
Lenalidomide	No	No	Substrate	Fasting (reduced Cmax with food)	No effect
Thalidomide	No	No	-	Minor (<10%) changes in AUC and Cmax with high-fat meal	No effect
Bortezomib	Yes	Poor inhibitor	Not substrate	IV (NA)	Enhanced (potential)
Carfilzomib	No	Weak inhibitor[c]	Substrate/Inhibitor	IV (NA)	Enhanced (potential)

AUC indicates area-under-the-curve; Cmax, maximum or peak concentration; IV, intravenous; NA, not applicable; PK, pharmacokinetic.

[a]CYP3A4 inducers (eg, St. John's Wort, phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital) and inhibitors (eg, grapefruit juice, ketoconazole, itraconazole, clarithromycin, atazanavir, nefazodone, saquinavir, telithromycin, ritonavir, indinavir, nelfinavir, voriconazole, conivaptan) should be used with caution in general when administered with agents that are major CYP3A4 substrates. Other CYP3A4-metabolized drugs (eg, triazolo-benzodiazepines, dihydropyridine calcium channel blockers, certain HMG-CoA reductase inhibitors, etc.) may interact with agents with inhibitory/inducing activity. For more information, fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093664.htm

[b]Inhibitors of P-glycoprotein (ABCB1) such as verapamil, itraconazole, ketoconazole, clarithromycin, erythromycin, diltiazem, conivaptan may increase the serum concentration of sensitive substrates such as aliskiren, ambrisentan, colchicine, dabigatran etexilate, digoxin, everolimus, fexofenadine, imatinib, lapatinib, maraviroc, nilotinib, bosutinib, posaconazole, ranolazine, saxagliptin, sirolimus, sitagliptin, tolvaptan, topotecan, rivoraxaban. For more information, www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093664.htm

[c]No effect on primary human hepatocytes or not expected to be clinically relevant on dosing schedule at therapeutic plasma concentrations.

[d]no clinically significant interaction with potent inhibitor (eg, itraconazole, ketoconazole).

Despite the spongiotic reaction with lymphocytic and eosinophilic infiltration in skin biopsies suggestive of drug hypersensitivity rash, this toxicity appeared not to be responsive to glucocorticoid therapy and only resolved upon vemurafenib interruption. A unique delayed dermatologic reaction that can appear or worsen days after drug

discontinuation has been observed with PI3K inhibitors (unpublished data).[31,32] This drug reaction is responsive to the use of corticosteroids and antihistamines (if rash is pruritic). Figure 4 shows a typical appearance of a moderately severe rash from a PI3K inhibitor.

Palmar plantar erythrodyesthesia or hand–foot skin reactions (HFSR) are commonly associated with multikinase inhibitors targeting VEGFR and other angiogenic targets, and are thought to represent a Koebner phenomenon. This refers to provocation of skin lesions by various triggers, mainly trauma, but also includes other causes of epidermal injury or inflammation such as exposure to extreme temperature (either freezing or burns), repetitive motion (friction or pressure forces) or other exposures, such as radiation or ultraviolet light.[33] Figure 5 is a representative example of HFSR associated with a multikinase inhibitor. The clinical presenting features of focal blister and callus-like formation in the palms and soles exposed to mechanical trauma with the targeted agents are distinct from the diffuse erythema with exfoliative desquamation and erosive lesions which can affect intertriginous skin seen in the HFSR associated with cytotoxic agents such as anthracyclines and pyrimidine analogues.[34] Shared histological findings on skin biopsy for both include keratinocyte necrosis, dilated blood vessels in the dermis with perivascular lymphohistiocytic infiltrates, parakeratosis, and epidermal acanthosis.[34-36] Chemotherapy-induced HFSR is thought to arise in part due to local toxicity of the concentrated excretion of the chemotherapy agents from eccrine sweat glands.[37,38] This is not consistently demonstrated with HFSR associated with VEGFR TKIs.[39,40] Nonetheless, the HFSR associated with either cytotoxic chemotherapy or the VEGFR TKIs is known to be worsened by combination therapy with bevacizumab.[41-43] Interestingly, however, HFSR is not typically seen with bevacizumab monotherapy, suggesting that although the VEGF pathway is contributory, isolated VEGF inhibition alone is insufficient to cause HFSR. This hypothesis is supported by the fact that the incidence of HFSR is higher with multikinase inhibitors compared to bevacizumab.

Pigmentation disorders, typically depigmentation of the hair and of the skin as well in a few instances, is commonly reported in patients receiving agents that include c-KIT in their spectrum of inhibition, such as imatinib, dasatinib, sunitinib, and pazopanib.[44] This effect is reversible upon drug discontinuation and appears to be dose- and treatment duration-dependent. It is thought that the role of the c-KIT-MITF (microphthalmia-associated transcription factor) pathway in melanin production underlies this depigmentation effect.[45] Reduced pigmentation of hair and skin has also been reported for the MEK inhibitor selumetinib.[46] Among patients with skin changes who underwent skin biopsies, the number of melanocytes was not reduced nor was there a quantitative change in MITF in melanocytes.[46] Although the mechanism remains speculative, it is thought that depigmentation arises from the loss of MAPK pathway activation, as MAPK pathway is utilized by physiologic c-KIT-MITF signaling in promoting pigment production.[47] In contrast, paradoxical hyper- or repigmentation with imatinib has been rarely described although the mechanism is not understood.[48-51] Drug-induced dark blue-gray pigmentation thought to be related to hemosiderin deposition has also been reported anecdotally with vandetanib.[52] The mechanism underlying this is also not known.

Alopecia is a common side effect with the smoothened receptor (SMO) inhibitor, vismodegib, which is an on-target effect as hedgehog signaling is essential for hair development.[53] It is commonly seen as well with agents that can inhibit BRAF, most often with vemurafenib but also seen with sorafenib and dabrafenib. Because VEGF is a major mediator of hair follicle growth and cycling,[54] alopecia may be seen to varying extent as well with TKIs that have VEGFR inhibitory activity. It should be noted though that the incidence of alopecia with these compounds is relatively infrequent in comparison to classical cytotoxic agents. Compounds that affect proteins regulating cell cycle and mitoses, such as aurora kinase inhibitors and polo-like kinase inhibitors exhibit toxicity profiles similar to traditional cytotoxic agents. Not surprisingly, alopecia is a frequently observed adverse effect with many of these particular agents.

Cardiovascular

Cardiovascular adverse effects, which are generally, but not always, reversible upon drug discontinuation, are common with a number of novel agents. These adverse effects include left ventricular (LV) dysfunction (either asymptomatic or symptomatic), conduction abnormalities/arrhythmias, arterial hypertension, and thromboembolism.

LV Dysfunction

The exact mechanisms underlying LV dysfunction for most of these agents are not well understood. One of the earliest agents to be studied in this regard was trastuzumab, an anti-HER2 antibody. Mouse models have demonstrated the importance of HER2 signaling in cardiomyocyte function and that loss of function results in dilated cardiomyopathy.[55,56] The estimated absolute increase in risk of LV ejection fraction (LVEF) reduction and congestive heart failure (CHF) were 7.2% to 7.5% and 1.6% to 1.9% respectively in breast cancer patients, whether with early or advanced stage of disease, with the greatest risk of CHF — up to 27% — in combination with anthracycline-based chemotherapy.[57-59] Although experience with pertuzumab, another antibody that binds to a different HER2 domain distinct from trastuzumab, is not as extensive, recent pooled analysis demonstrated rates of cardiac events similar to the trastuzumab experience, whether pertuzumab was

administered alone or in combination with trastuzumab. Asymptomatic LV dysfunction was seen in 6.9% and 6.5% with this agent alone or in combination with trastuzumab, respectively, whereas symptomatic CHF developed in 0.3% and 1.1% with pertuzumab alone or in combination with trastuzumab, respectively, suggesting no notable increase in cardiac side effects with this combination.[60] Lapatinib, an oral dual EGFR/HER2 TKI, in comparison induces asymptomatic and symptomatic cardiac events in 1.4% and 0.2%, of treated patients, respectively.[61] Given the much lower rate of cardiotoxicity with lapatinib, an alternate mechanism, such as the cardioprotective effect of 5′-adenosine monophosphate-activated protein kinase (AMPK) activation induced by lapatinib but not trastuzumab, has been proposed to account for the differential cardiotoxicity profile.[62] There are no measures proven effective in preventing cardiotoxicity with these agents. The optimal strategy, such as frequency and method used, in monitoring cardiotoxicity has yet to be established as current screening methods, eg, echocardiography or multiple gated acquisition (MUGA) scanning, blood markers of myocardial injury such as troponin, NT-proBNP, and circulating endothelial progenitor cells, novel imaging techniques such as cardiac magnetic resonance and molecular imaging, either lack adequate predictive power or are yet to be validated.[63]

LV dysfunction has also been reported in association with VEGF pathway and ABL kinase inhibitors. Mouse models demonstrate the importance of VEGF in maintaining cardiomyocyte function, whereas treatment with these agents can result in direct cardiomyocyte death.[64-66] The off-target inhibition of AMPK appears to underlie this effect for the multikinase inhibitor sunitinib, because restoring AMPK activity reduces its toxicity in cardiomyocytes.[67] In contrast, c-ABL was shown to be the main target mediating cardiomyocyte toxicity of imatinib, whereas concomitant JNK inhibition reduces cardiotoxicity.[64,67,68] However, there is disagreement as to whether AMPK or c-ABL is the principal mediator of cardiotoxicity (eg, in vitro concentration required to inhibit AMPK is much greater than what can be achieved in clinic with therapeutic doses), with subsequent studies suggesting instead the composite effect on multiple kinases, because lack of kinase selectivity and specificity is highly correlated with risk of cardiomyocyte damage from small molecule kinase inhibitors.[69-72] Inhibition of some or all members of a panel of candidate kinases such as ALK, FGFR4, MEK1, and MEK2 were correlated with cardiomyocyte damage.[71] Other AMPK and c-ABL kinase-independent effects include direct mitochondrial damage caused by sorafenib and lysosomal dysfunction and endoplasmic reticulum stress by imatinib, leading to mitochondrial-induced cardiomyocyte death. In addition, prolonged proteasome dysfunction can lead to heart failure in patients receiving bortezomib or carfilzomib. These effects are thought to be mediated through maladaptive calcineurin signaling in the cardiomyocyte.[73-75] Peripheral edema, including periorbital and facial edema, and weight gain have been reported in patients receiving MEK inhibitors and inhibitors of the MET pathway such as crizotinib, cabozantinib, foretinib, and onartuzumab. Although many studies did not routinely include serial assessment of LV function, the peripheral edema in some cases may potentially be a manifestation of reduction in LV ejection fraction, seen with varying frequency in MEK inhibitors (eg, 8% in early-phase trials of trametinib). A preclinical model of MEK inhibition in cardiomyocytes demonstrated that the resulting inhibition of ERK activation, in conjunction with activation of p38 and the JNK pathway, resulted in cardiomyocyte apoptosis and reduced functional recovery upon ischemic stress.[76] Similarly, MET signaling is crucial in reducing cardiomyocyte apoptosis in hypoxic/ischemic conditions, such that its inhibition increases infarct size and mortality in a preclinical in vivo model.[77] In addition, MET signaling is important in the regulation of cardiac remodeling and cardiovascular angiogenesis.[78] The IGF-1R/PI3K/AKT axis is also involved in cardioprotection during reperfusion injury and is implicated in both physiologic (eg, PI3Kα-mediated normal hypertrophy such as with exercise) and pathologic cardiac regeneration (e.g. pathological cardiac remodeling and fibrosis mediated by PI3Kγ signaling).[79] Indeed, the phase 3 study of the IGF-1R monoclonal antibody, figitumumab, in combination with chemotherapy as first-line therapy in advanced non–small cell lung cancer (NSCLC) demonstrated a higher incidence of cardiac events (all grades) in the experimental arm, with fatal cardiovascular adverse effects in 3% compared to 1.2%, of patients in the experimental arm and the control arm, respectively.[80] Cardiac safety endpoints should thus be taken into consideration in the development of inhibitors of this pathway.

Hypertension

Hypertension is a classic on-target adverse effect resulting from VEGF pathway inhibition, as seen in multiple clinical trials with bevacizumab (anti-VEGF mAb), aflibercept (VEGF trap) and VEGFR TKIs, including the multikinase inhibitors sorafenib, sunitinib, and regorafenib.[81] This effect is thought to be mediated through disruption of nitric oxide–activated VEGFR2 signaling, which in physiologic conditions results in vasodilation. Posterior reversible encephalopathy syndrome, a clinicoradiologic diagnosis in which patients present with headaches and visual changes, with or without seizures, and malignant hypertension in association with a classic MRI appearance, is a rare but severe manifestation associated with these agents. As the name implies, signs and symptoms are generally reversible upon discontinuation of the offending agent as well as optimization of blood pressure control, although residual neurological deficits may rarely persist. Another syndrome

associated with hypertension is thrombotic microangiopathy (TMA), marked by renal dysfunction, worsening proteinuria, varying degrees of hemolytic anemia, and thrombocytopenia. This is also generally reversible upon drug cessation. It has been demonstrated that local reduction of VEGF in the kidney is sufficient to trigger TMA.[82] The risk for this complication appears to be increased in patients with renal cell carcinoma (RCC), particularly when treated with a combination of anti-VEGF pathway agents.[43,83] Thus, blood pressure monitoring and prompt institution of antihypertensive agents are recommended when treatment with these agents is initiated. If there are no contraindications, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers are preferred agents as they also reduce the associated proteinuria seen with these agents. In contrast, orthostatic hypotension seen with thalidomide and bortezomib is thought to be a manifestation of autonomic dysfunction as part of the spectrum of drug-induced neuropathy with these agents.

Conduction Abnormalities

Sinus bradycardia is a known adverse effect of thalidomide, although its actual incidence, ranging from 0.12% in initial postmarketing surveillance studies to a little more than 50%, is not well-documented due to lack of systematic monitoring and uniform definition.[84] In a small single-arm phase 2 study of thalidomide monotherapy for multiple myeloma, up to 26% of patients were documented to have sinus bradycardia, 5% of whom were deemed to have CTC of at least grade 3 severity.[85] Symptomatic thalidomide-induced bradycardia has been reported in up to 19% of patients in another small retrospective study.[84] Sinus bradycardia (heart rate $\leq$ 45 beats/minute) was documented in 19% of patients who received crizotinib in a small series of patients and appears to be a pharmacodynamic marker associated with higher response rate.[86] Dose-related conduction abnormalities such as bradycardia and atrioventricular (AV) block without clinically significant sequelae have also been documented for HSP90 inhibitors and MET inhibitors such as tivantinib. The pathophysiology and evaluation of QT prolongation has been recently reviewed.[87] Agents with demonstrated dose- or concentration-dependent QT prolonging effects include several kinase inhibitors (eg, sunitinib, sorafenib, pazopanib, vandetanib, nilotinib, dasatinib, vemurafenib, crizotinib) and histone deacetylase (HDAC) inhibitors (eg, romidepsin, panobinostat). In a placebo-controlled 2-period cross-over study to assess its effect on the QT interval, vorinostat did not appear to prolong the corrected QT interval after a single 800-mg dose. QT prolongation is linked to direct inhibition of the hERG channel and screening for this occurs in the early stages of drug discovery.[88] Nonetheless, QT prolongation can be dose-limiting, and can lead to discontinuation of early drug development as exemplified by the PIM kinase inhibitor SGI-1776, and the cyclin-dependent kinase inhibitor, AT7519. While mostly without clinically significant or symptomatic sequelae, clinicians have to be cognizant of QT prolongation, which can be potentially intensified and can lead to potentially fatal arrhythmias when certain other medications are prescribed (eg, beta-blockers exacerbating bradycardia), or when there are concurrent medical issues (eg, underlying poor LV function or concomitant hypokalemia and/or hypomagnesemia due to diarrhea leading to torsades de pointes in the setting of QT prolongation).

Hemorrhage and Thromboembolic Events

The risk of arterial ischemic/thromboembolic events (ATE), but not venous thromboembolism, is increased with inhibitors of the VEGF pathway.[89,90] A pooled analysis demonstrated an absolute increase of 2.1% in the incidence of ATE for patients receiving bevacizumab with chemotherapy compared with chemotherapy alone (3.8% versus 1.7%).[89] Multivariate analyses showed that age of 65 years or older, history of ATE and exposure to bevacizumab were associated with ATE across the entire population. A similar analysis for the VEGFR kinase inhibitors sorafenib and sunitinib demonstrated an incidence of 1.4%, representing a 3-fold increased risk compared with control patients.[90] Mechanisms postulated mainly implicate the role of VEGF and nitric oxide in maintaining the integrity of endothelial cells. Another mechanism demonstrated was activation of platelet aggregation and degranulation to trigger the thrombosis cascade when bevacizumab complexes with the platelet FcγRIIa receptor.[91] However, the risk of serious hemorrhage with these agents is just as high as, if not higher than, the risk for ATEs. The overall incidence of severe hemorrhagic events with bevacizumab was 2.8%, with higher risks seen in patients with NSCLC, RCC, and colorectal cancer.[92] Fatal adverse effects with chemo-therapy combined with bevacizumab were 2.5%, compared with 1.7% for chemotherapy alone. In a meta-analysis, hemorrhage was the highest cause of mortality (1.3%).[93] Similarly, the incidence of hemorrhage (all grades) for VEGFR kinase inhibitors sorafenib and sunitinib was 16.7%, with 2.4% incidence for serious high-grade events.[94] It is to be noted that patients with known bleeding diathesis, active bleeding (eg, hemoptysis), or high-risk tumor features (eg, cavitary mass or centrally located thoracic mass) are generally excluded from clinical trials to mitigate this risk. There are thus currently no routine recommendations for prophylaxis of hemorrhagic or thromboembolic events, and a better understanding of risk stratification is needed before prophylactic treatments can be recommended. Rapidly progressive peripheral arterial occlusive disease has been recently described with nilotinib in patients with preexisting risk factors.[95,96] However, a true increased incidence compared to a control group in randomized studies has yet to be demonstrated.

In contrast, an increased risk of venous thromboembolism (VTE) is a well-established fact with the use of thalidomide and its analogues when combined with other agents such as

dexamethasone or doxorubicin (the exception is bortezomib, which appears to ameliorate the risk of thromboembolism with thalidomide).[97,98] There is a higher risk in newly diagnosed patients, particularly during the first 4 to 6 months.[98] Risk-stratified prophylaxis is thus recommended for multiple myeloma patients who are prescribed these agents to reduce the risk of VTE to at least below 10%.[98,99] Aspirin is an effective alternative to low-molecular weight heparin among patients with a low thromboembolic risk profile.[97,100] There are conflicting reports on the risk of VTE with the use of bevacizumab, with one meta-analysis that demonstrated an increased risk of VTE with bevacizumab treatment compared with control but no increased risk in another meta-analysis cited earlier.[89,101] More recently, a meta-analysis suggested an increased risk of VTE, but not ATE, when monoclonal antibodies against EGFR (but not TKI) are combined with chemotherapy.[102]

Pulmonary

Drug-induced noninfectious pneumonitis/interstitial lung disease, ranging from asymptomatic radiographic findings of nonspecific inflammatory infiltrates to fulminant cases have been reported in 0.1% to 15% of patients with hematological malignancies treated with novel antineoplastic agents.[103] This toxicity is frequent among patients with solid malignancies treated with mTOR inhibitors. Patients typically present with cough and dyspnea, with or without accompanying fever. Pneumonitis usually occurs in the first 6 months of treatment and may be detected radiographically as early as 2 months.[104] CT evidence of pneumonitis has been reported in up to 45% of patients receiving temsirolimus at 13 months.[105] Radiographic findings range from the most common appearance consisting of patchy diffuse ground-glass opacities, to classic drug-induced interstitial lung disease (ILD) patterns such as those resembling acute interstitial pneumonitis (AIP) and ARDS.[104,105] Differential diagnoses include infection and disease progression with lymphangitic spread. Similar to skin rash being a potential correlate of treatment response with EGFR inhibitors, the radiographic appearance of pneumonitis has been recently correlated with drug efficacy and disease stability in metastatic clear cell renal cancer patients.[106] Thus, expert opinion based on empiric observation is to continue the administration of mTOR inhibitors with close surveillance of patients who are asymptomatic or have a mild cough without associated dyspnea. If patients start to develop dyspnea, dose reduction with or without institution of corticosteroids should be considered. In patients with severe or life-threatening symptoms, drug interruption or discontinuation in addition to pulmonary evaluation with bronchoscopy and bronchoalveolar lavage (BAL) to distinguish infectious causes are strongly recommended along with empiric treatment with corticosteroids if high-resolution CT chest is nondiagnostic.[104] BAL findings may also help distinguish the pattern of lung injury and further management (lymphocytosis along with low CD4:CD8 ratio ≤ 1 in hypersensitivity pneumonitis [normal or high ratio does not exclude diagnosis]; hemosiderin-laden macrophages in diffuse alveolar hemorrhage, neutrophilia and atypical type II pneumocytes with direct cytotoxic reaction, and so forth).[107] The etiology is unclear and risk factors have yet to be definitely ascertained. Pneumonitis has also been reported with a few pan-PI3K inhibitors in early-phase clinical trials.[108,109] Although this is suspected to be potentially a class effect, a true causal relationship cannot be ascertained due to limited data at this time.

In contrast to mTOR inhibitors, ILD is rarely encountered but is also a potentially life-threatening complication among patients receiving EGFR inhibitors. Postmarketing surveillance of either EGFR TKI or monoclonal antibody drugs reported an incidence of 1.2% to 1.9% in Japanese patients versus 0.3% for the rest of the world.[106,110] Risk factors suggested include older age and preexisting interstitial pneumonia.[111] Preclinical in vivo models suggest that the mechanism maybe related to reduced surfactant protein A expression in lung tissues with EGFR inhibition.[112] Furthermore, in the setting of acute lung injury, EGFR inhibition promoted upregulation of genes that result in prolonged inflammation.[113] The reason for the higher frequency seen in Japan is unknown. Drug-induced ILD due to bortezomib, thalidomide and its analogues, imatinib, MET inhibitors (crizotinib, tivantinib) and HSP inhibitors such as 17DMAG has also been reported. The exact mechanism is unclear though management is similar to that recommended for mTOR inhibitors.

Pleural effusion is seen in 16% to 54% of patients treated with dasatinib therapy, and responds to the use of steroids along with dose interruption. This appears to be both a dose- (higher risk with actual mean dose > 100 mg/day) and schedule-dependent effect (higher occurrence using the twice-daily dosing schedule).[114,115] The pathogenesis is unclear although blockade of PDGFR-β has been implicated as the cause of fluid retention seen with multikinase inhibitors.[116] Pleural effusion has also been reported in 8% of patients treated with bosutinib, the majority of whom experienced this toxicity with prior TKI therapies.[117]

Another rare toxicity is pulmonary arterial hypertension (PAH), associated with dasatinib with a reported incidence of 0.45% to 1.2%.[118,119] The pathogenesis is unclear and attributed to off-target effects. Improvement is usually observed upon withdrawal of treatment. Other ABL inhibitors do not appear to have this associated effect. PAH has also been reported in patients treated with carfilzomib. Causality and pathogenesis are unclear.

Metabolic/Endocrine

Hypothyroidism is the most common treatment-emergent endocrinopathy associated to date with targeted therapies, commonly the multikinase inhibitors.[81] This has been classified loosely into 2 types: recurrent hypothyroidism in

thyroidectomized patients with known hypothyroidism controlled with exogenous hormone supplementation and de novo hypothyroidism.[120] The former has been seen with agents such as imatinib, sorafenib, sunitinib, and bexarotene, manifested as increasing TSH levels, as early as within 2 weeks of therapy. This may be attributed to enhanced T3 and T4 metabolism due to their clearance by increased activity of type 3 deiodinase.[121,122] In the case of bexarotene, increased thyroid hormone metabolism was not deiodeinase-dependent but attributable instead to hepatic mechanisms, such as increased sulfation.[123] Another mechanism suggested recently is the dose-dependent inhibition of the thyroid hormone transporter MCT8 in the pituitary and other organs by the previously mentioned multikinase agents, as well as the second-generation ABL inhibitors dasatinib and bosutinib. The inhibition of MCT8 is felt to explain the TSH elevation from loss of thyroid hormone feedback at the pituitary/hypothalamus level in previously thyroidectomized patients and the reversibility of the thyroid hormone abnormalities upon withdrawal of the agents.[124]

In the case of bexarotene, de novo hypothyroidism is centrally mediated in the pituitary by suppression of transcription of the B-subunit of TSH and direct inhibition of TSH secretion of the thyrotrophs.[120] Because this side effect is almost universally observed in patients undergoing bexarotene treatment, levothyroxine should be started simultaneously with bexarotene, along with weekly measurement of free T4 level for the first 2 months, followed by periodic monitoring 1 to 2 months thereafter.[120] The mechanism behind de novo hypothyroidism in patients with normal thyroid function being treated with multikinase agents, as well as thalidomide and its analogues, is unclear. Because this is seen commonly across various TKIs with activity against VEGFR, thyroid toxicity is thought to arise from attrition of normal thyroid follicular cells due to inhibition of angiogenesis, with resultant thyroidal capillary regression.[124] Other vascular-mediated mechanisms proposed include impaired iodine uptake,[125] and ischemic thyroiditis, with a period of thyrotoxicosis preceding the development of hypothyroidism.[120] More recently, inhibition of RET kinase (eg, by sunitinib, sorafenib, vandetanib) is also hypothesized to contribute to hypothyroidism based on its physiologic role in the development and function of parafollicular cells, which in turn regulate/stimulate follicular thyroid cells in a paracrine fashion. Regardless of the mechanism, it is recommended that pretreatment TSH levels be obtained, followed by monitoring every 1-2 months, with appropriate institution or dose adjustment of replacement therapy and intervals for testing as applicable.

Secondary hyperparathyroidism, characterized by a relative reduction in serum phosphate and in urinary calcium along with an increase in PTH levels compared to baseline pretreatment levels, with or without reduction in blood calcium level, has also been documented with the multikinase agents sorafenib, sunitinib, imatinib, and nilotinib. The biochemical changes did not progressively worsen with long-term therapy and bone mineral density (BMD), measured prospectively in patients receiving imatinib and nilotinib, was generally stable to slightly increased over a 2-year period.[126,127] These blood level and BMD changes are thought to reflect sequestration of these minerals into the bone by the antiosteoclastogenic effect and promotion of osteoblast differentiation through PDGFR inhibition by these agents.[128] Whereas there is a corresponding increase in the level of 1,25-dihydroxyvitamin D3 in response to the PTH elevation with the latter 3 agents, levels were abnormally low in sorafenib-treated patients. It has thus been suggested that routine monitoring of this biochemical panel and BMD may not be necessary for patients receiving imatinib, and by extrapolation, to agents manifesting a similar profile of changes. However, the hypovitaminosis D in association with hyperparathyroidism is thought to contribute to sorafenib-induced sarcopenia and may lead to osteomalacia.[129,130] Vitamin D supplementation can normalize the hypophosphatemia and PTH levels.[131,132] A prospective study is warranted to determine the clinical significance of biochemical monitoring and vitamin D supplementation for sorafenib-treated patients. Hypophosphatemia is also a frequent side effect of mTOR inhibitors.[133] A preclinical study of rapamycin showed that its use was accompanied by phosphaturia due to down-regulation of phosphate carriers in the proximal tubules along with increased 1,25-dihydroxyvitamin D3 levels but no alteration in PTH concentrations.[134] Moreover, mTOR inhibitors can inhibit osteoclast activity and promote osteogenesis in vitro.[135-137] Dose-dependent hypophosphatemia has also been reported with multiple other agents, such as HDAC, MET and selective ALK inhibitors, although long-term skeletal effects are unclear. Periodic monitoring, with more frequent measurements in moderate to severe deficiency, has been recommended, along with phosphate supplementation. Drug interruption is indicated only in severe cases.[133]Although blood mineral levels are not affected, an anabolic effect in the bones is observed with proteasome inhibitors. This is thought to be directly through inhibition of osteoclast differentiation, and resorption and stimulation of osteoblast differentiation by disrupting RANKL-induced NF-kB signaling.[138]

Central hypogonadism which occurs rapidly within 2 to 3 weeks of treatment initiation, as documented by reduction in testosterone, FSH and LH levels, has been recently reported in several male patients receiving crizotinib. This was reversible upon treatment interruption.[139] The exact mechanism is unknown. The impact on quality of life and potential benefit of testosterone replacement, as well as comparable effects on female patients, are areas for future investigation. Hypogonadism is also a potential side effect of agents

modulating the T-cell response (discussed in the immunologic subsection).

Hyperglycemia and hyperlipidemia are anticipated class effects of agents affecting the PI3K/AKT/mTOR pathway as this pathway mediates signals downstream of the insulin receptor.[140] Of interest is preclinical evidence suggesting that metabolic derangements such as hyperglycemia appear to be worse with PI3K inhibition alone compared to dual PI3K/mTOR inhibition in the presence of insulin resistance.[141] Hyperlipidemia is also an anticipated adverse effect of retinoids and rexinoids. This arises from RXR (retinoid X receptor)-mediated expression of genes implicated in lipogenesis through heterodimerization with another nuclear LXR (liver X receptor).[142] Mild to moderate hypercholesterolemia appears to be a class effect as well of janus kinase (JAK) inhibitors, as this was also seen in clinical trials of JAK inhibitors developed for inflammatory conditions such as rheumatoid arthritis or ulcerative colitis. Close monitoring is recommended, with institution of oral hypoglycemic agents and/or insulin for hyperglycemia/diabetes according to standard practice. Collaboration with an endocrinologist is encouraged. Lipid-lowering therapies, such as fibrates or HMG CoA reductase inhibitors are indicated to avoid pancreatitis arising from extremely high levels of triglycerides or cholesterol, although there is no uniform approach in cholesterol and triglyceride management in the metastatic disease setting, because existing clinical guidelines relate to long-term cardiovascular outcomes. Unrecognized hypothyroidism may also complicate the dyslipidemia seen with retinoids/rexinoids. Correcting hypothyroidism will facilitate management of hypertriglyceridemia in this setting. Pretreatment with fenofibrate has been recommended before starting bexarotene, whereas gemfibrozil is not recommended due to drug interactions (higher plasma bexarotene level) leading to increased triglyceride level.[143] Because these metabolic changes are rarely acutely life-threatening, dose modification or treatment interruption is generally implemented only in settings with clinically severe presentations or if metabolic changes remain uncontrolled despite institution of pharmacologic agents to achieve glycemic and lipid control.

On the other hand, reduction in blood glucose or improvement in glycemic control in both nondiabetic and diabetic patients, independent of other lifestyle or dietary changes, has been reported in patients taking the multikinase inhibitors imatinib, dasatinib, sorafenib, and sunitinib. Results from a preclinical murine model strongly suggested that this may be mediated through PDGFR, and to a minor extent c-KIT inhibition.[144] More recently, chemical structure analysis suggests an additional mechanism of imatinib acting as a ligand to modulate farnesoid X receptor (FXR), a transcription factor belonging to the nuclear receptor superfamily that is involved in glucose and lipid homeostasis.[145] Thus, diabetic patients who are prescribed these medications should monitor blood glucose routinely as dose reduction or discontinuation of their antihypoglycemic regimen maybe required to avoid symptomatic hypoglycemia.

Hypomagnesemia is a common metabolic abnormality seen with monoclonal antibodies against EGFR. Pooled analyses across seven randomized trials demonstrated an overall incidence of 27.2% versus 5.6% in the control arm.[146] A prospective investigation showed defective renal magnesium reabsorption, with hypomagnesemia correlated positively with total treatment duration and inversely with age and baseline serum magnesium concentrations.[147] This renal magnesium wasting is thought to arise from the role of EGF in regulating the activity and distribution of transepithelial magnesium channel TRPM6. In addition, it has been discovered that a point mutation in the EGFR gene causes isolated hypomagnesemia.[148,149] This is a reversible finding, with resolution within 2 to 3 months of treatment cessation in the absence of supplementation. During active treatment, however, weekly intravenous administration of magnesium could not sustain normal magnesium levels as correction is transient and may last no more than 48 hours.[147] Thus, a more frequent replacement schedule (eg, daily or every other day) is needed for severe hypomagnesemia, particularly for symptomatic or high-risk patients. Hypomagnesemia is less commonly encountered with EGFR TKIs, which may be attributable to the observation that typical doses cannot achieve sufficient plasma concentrations to inhibit EGF-induced TRPM6 density and plasma membrane trafficking.[150]

A number of other biochemical abnormalities without clinically significant sequelae in the majority of patients, such as hyperamylasemia and/or hyperlipasemia are seen with various agents. Creatine kinase (CK) elevation, mostly asymptomatic and without associated troponin abnormalities, has been reported in 18% to 50% of patients in early-phase testing of dual RAF/MEK or MEK inhibitors.[151-153] A small prospective study in solid tumor patients demonstrated that CK elevation is more frequent with imatinib than other TKIs.[154] Correlation with symptomatic myalgias/muscle cramps is not consistently demonstrated.[154,155]

Hematologic

Cytopenia is seen with targeted therapies, with the frequency and severity varying according to drug class and specific agents. Because the kinases c-KIT and FLT-3 are important in the development of hematopoietic stem cells and early progenitor cells, relative differences in potency against these targets across various multikinase agents have been proposed as the underlying etiology of the variable clinical myelosuppression observed (eg, sunitinib causing more neutropenia and thrombocytopenia in comparison to pazopanib).[156] Depending on the agent, this maybe a dose-

and schedule-dependent effect, as exemplified by the reduced toxicity, myelosuppression included, when dasatinib is administered on the equally efficacious 100 mg once daily regimen compared to the approved dosage of 70 mg twice daily.[115] Moreover, this knowledge has been used to develop agents in hematologic malignancies, such as sorafenib for FLT3-internal tandem duplication positive leukemia.[157] Current data also suggest that the PI3K/AKT/mTOR pathway is activated by cytokines to drive proliferation of hematopoietic cell lines. It is therefore not surprising that hematological toxicities can be observed with inhibitors of this pathway.[158-161] Similarly, as most hematopoietic cytokines transmit their signals mainly through the JAK/STAT pathway,[162] anemia and thrombocytopenia are the 2 most common side effects seen with the selective JAK1/2 inhibitor ruxolitinib.[163] In contrast, the relatively lower frequency of myelosuppression with inhibitors of the PI3K/AKT/mTOR pathway is thought to be due to the presence of endogenous PIM kinases that can support the growth and survival of nontransformed hematopoietic cells despite exposure to pharmacologic doses of an mTOR inhibitor, such as rapamycin.[164] Agents that affect proteins regulating cell cycle and mitosis, such as aurora kinase inhibitors, polo-like kinase inhibitors, and cyclin-dependent kinase inhibitors exhibit toxicity profiles similar to traditional cytotoxic agents, with hematologic toxicities such as neutropenia and thrombocytopenia comprising the most common side effects encountered that maybe dose-limiting and schedule-dependent (eg, continuous versus intermittent administration). Severe neutropenia is also rarely (<10%) seen in patients treated with MET and ALK inhibitors though the mechanism behind this is not known.[165-167]

Reversible thrombocytopenia is the most common dose-limiting hematologic toxicity of HDAC inhibitors.[168] Mechanistic studies reveal that HDAC inhibitors cause megakaryocytic hyperplasia and induce thrombocytopenia by delaying megakaryocyte maturation and reducing thrombopoiesis without causing platelet apoptosis through transcriptional repression of the erythroid transcription factor, GATA-1 and other hematopoietic factors, likely mediated by inactivation of HDAC1 and HDAC2.[168-172] Reduction in the RHO-GTPase proteins RAC1, RHOA and CDC42 is also thought to underlie the reduction in proplatelet formation, thus leading to thrombocytopenia.[168] Despite the associated high levels of thrombopoietin seen as a physiologic response to the thrombocytopenia, the use of a thrombopoietin peptide mimetic appears to ameliorate this toxicity in a mouse model.[168] This transient thrombocytopenia followed by rapid rebound recovery when treatment is stopped, including changes in thrombopoietin levels and megakaryocyte appearance in the bone marrow, is similar to what is observed with proteasome inhibitors (except marizomib) although the molecular pathogenesis is not elucidated.[172,173] In contrast, the mechanism-based dose-dependent thrombocytopenia observed with BCL2-inhibitors (eg, obatoclax, navitoclax) is related to platelet apoptosis and decreased platelet survival in the circulation due to abrogation of BCL-XL function.[174] Thrombocytopenia that appears in the first 4 weeks of treatment appears to be circumvented by starting at a lower lead-in dose for 1 to 2 weeks before increasing to the full therapeutic dose. The rationale is that selective early apoptosis of older platelets results in the generation of a younger platelet population more resistant to apoptosis.[175]

For solid tumor malignancies, cytopenias are generally managed by dose interruption and/or dose modification, as this toxicity is viewed as an undesired off-target effect on normal hematopoietic precursors. However, in patients with hematological malignancies, myelosuppression may reflect an on-target effect on the malignant clonal population alongside inadequate regeneration of normal hematopoietic progenitors. Interestingly, myelosuppression has been found to be an independent adverse prognostic factor for achieving cytogenetic response in CML patients.[176] Prophylactic use of granulocyte-colony stimulating factor (G-CSF) has been advocated to minimize associated neutropenic infections when targeted agents are used in selected high-risk hematologic cancer patients. This includes the use of targeted agents in combination with cytotoxic chemotherapy drugs such as alkylating agents or anthracyclines, advanced disease stage, extensive prior therapies and low baseline blood counts. G-CSF can also be used as reactive treatment when severe neutropenia arises to limit drug interruption.[176-178]

Neuropsychiatric

Neurotoxicity (such as hypersomnolence, dyssomnia, ataxia, dizziness) including altered mood disorders (such as anxiety and depression) have been reported with some MEK and PI3K inhibitors, respectively, with differences among individual drugs within a class potentially related to differential ability to cross the blood–brain barrier.[179-183] Neurotoxicity is also anticipated with agents whose structural scaffolds bear similarity to psychotropic agents such as benzodiazepines, exemplified by the aurora kinase inhibitors MLN8054 and MLN8237. The symptoms are generally reversible with drug discontinuation. Preclinical models in mice showed that either innate deficiency or extrinsic inhibition of PI3K or MEK signaling resulted in decreased cognitive ability and increased depression and anxiety, because PI3K and MEK signaling is important in regulating neurogenesis and memory. These effects are apparently mediated through regulating the concentrations of serotonin and mediating the effects of brain-derived

neurotrophic factors in the amygdala.[184-189] Postmortem examination in a small study showed an association between reduction in PI3K/AKT activity in the ventral prefrontal cortex and major depression disorder. As well, reduction of MEK1 catalytic activity in the prefrontal cortex and amygdala was seen in patients who committed suicide.[190] Of note, the preclinical models employing systemic treatment with PI3K or MEK inhibitors demonstrated that the cognitive and behavioral changes of PI3K or MEK inhibition could not be completely reversed with administration of antidepressant agents in mice with genetic susceptibility to depression/anxiety.[184,185] Thus, treatment guidelines generally indicate drug interruption for severe (CTC grade 3 or higher) symptoms or the lack of improvement in 1 to 2 weeks despite institution of psychotropic agents for a moderate (CTC grade 2) mood disorder.

Thalidomide, originally marketed as a sedative, initially causes somnolence in 75% of patients who commonly develop tachyphylaxis.[191] Other cental nervous system (CNS) effects include fatigue, mild tremors, anxiety, agitation, confusion and ataxia. Thalidomide principally causes cumulative dose-dependent distal sensory peripheral neuropathy even at low doses (25-50 mg) though this is characteristically marked by sensory loss or paresthesia. Pain is less often encountered in contradistinction to the neuropathic pain that is prominent with bortezomib.[191] In contrast, the thalidomide analogues lenalidomide and pomalidomide do not cause somnolence, and other neurological effects, including peripheral neuropathy, are rarely seen with its use. The molecular mechanisms responsible for these adverse effects are not well characterized. There are no pharmacologic agents with proven efficacy in preventing neuropathy, although gabapentin and similar agents have been used for symptomatic relief of symptoms. General guidelines, such as dose interruption and upon improvement, drug reinitiation with dose reduction, are typically implemented.

Treatment-emergent peripheral neuropathy associated with the reversible proteasome inhibitor bortezomib is recently thought to be a result of drug-specific damage to the dorsal root ganglion, related to inhibition of nonproteasomal off-target proteases, including HtrA2/Omi, a stress induced protease involved in neuronal cell survival, rather than a class effect.[192] This neuropathy is generally a reversible toxicity that can be managed with dose reduction/interruption, modified schedule (eg, once weekly versus twice weekly) or route of administration (subcutaneous route showing lower toxicity with similar efficacy).[193,194] There are no pharmacologic agents with proven efficacy in preventing neuropathy and thus the most effective approach is to adhere to general recommendations modifying dose, schedule or route of administration.[195] The lower rate of toxicity seen with the equipotent epoxyketone irreversible proteasome inhibitor carfilzomib is attributed to its greater selectivity for the chymotrypsin-like subunit of the proteasome, with minimal effect on nonproteasomal proteases such as serine proteases affected by bortezomib.[192] Marizomib, another irreversible proteasome inhibitor that inhibits both chymotrypsin-like and trypsin-like activity also does not induce significant peripheral neuropathy. However, it is associated with other neurotoxic effects, such as cognitive changes, transient hallucinations, dizziness and headache.[196]

Gastrointestinal/Hepatobiliary

Mucosal inflammation, ranging from oro-pharyngolaryngeal pain without evident erosions to frank stomatitis, and diarrhea are encountered across a wide spectrum of novel agents (inhibitors of EGFR/RAF/MEK pathway, multikinase VEGFR and ABL inhibitors, aurora kinase inhibitors, polo-like kinase inhibitors, PI3K/AKT/mTOR pathway inhibitors) as they affect, with varying potency, the physiologic processes of normal proliferation and repair of cells with rapid turnover that line the alimentary tract. Mechanism-based diarrhea associated with inhibitors of Notch signaling,[197,198] such as gamma secretase inhibitors, is thought to be due to the conversion of proliferative undifferentiated intestinal crypt cells into secretory goblet cells.[199] Regardless of etiology, management of diarrhea includes the proactive use of antidiarrheal/antimotility agents such as loperamide or diphenoxylate/atropine at the first sign of diarrhea to avoid life-threatening dehydration arising from poorly controlled diarrhea. Treatment is held for CTC grade 3 or higher diarrhea and hospitalization should be considered, in addition to routine management (eg, stool culture, screening for *Clostridium difficile* toxin). Use of octreotide in refractory cases may be considered, similar to its use in chemotherapy- or radiation-induced diarrhea. In contrast, constipation seen with thalidomide is thought to be related to autonomic neuropathy induced by damage to small fibers.[195] Routine prophylactic use of stool softeners and/or laxatives is recommended with initiation of thalidomide treatment.

Isolated hyperbilirubinemia (due to the unconjugated fraction) associated with several kinase inhibitors (eg, erlotinib, sorafenib, regorafenib, pazopanib, nilotinib) may be related to their ability to inhibit UGT1A1 (uridine-diphosphoglucuronate glucuronosyltransferase 1A1).[200] Conversely, polymorphic variants in UGT1A1 may account for the isolated hyperbilirubinemia in these cases where an underlying Gilbert's syndrome is unmasked.[201-203] Treatment continuation maybe considered for this benign etiology. However careful monitoring should be undertaken as there may be other accompanying genotypes that can lead to reduced metabolism and high drug concentrations, leading to increased toxicity (eg, with sorafenib).[201]

Ophthalmologic

Ocular toxicity was classically associated as a class effect during the early development of MEK inhibitors (AZD6244 [selumetinib], 12.3%, CI-1040 22.4%, PD-0325901 33.3%, RO5126766, 50%, RO4987655, 27%; trametinib, 15%). Visual symptoms include blurred vision, halo vision, altered light perception, photophobia, diplopia, and epiphora. Because routine ophthalmologic examination became standard in the development of these agents, the blurred vision symptoms in some patients have been associated with the findings of central serous retinopathy, macular edema, or retinal vein occlusion. The underlying pathophysiology remains obscure although indirect evidence suggest that ERK activation is important for photoreceptor survival and that MEK inhibition results in apoptosis and loss of differentiation during photoreceptor development and in oxidative stress conditions.[204,205] The majority of events are reversible and either spontaneously resolve or improve with drug interruption and are of minor in severity (CTC grade 1). A preclinical model of retinal vein occlusion using PD0325901 suggests that MEK inhibition leads to retinal gene expression changes characteristic of oxidative stress and inflammatory response, with endothelium and blood–retinal barrier damage as well as prothrombotic effects.[206] Visual acuity reportedly improved after intraocular injection of anti-VEGF antibody. As retinal vein occlusion may result in permanent vision loss, it is imperative that assessment by an ophthalmologist be performed for patients who develop visual symptoms. In addition, a baseline evaluation and risk assessment prior to initiating treatment should be the standard approach for this class of drugs. Ocular toxicity of EGFR inhibitors are most commonly limited to corneal abnormalities (keratoconjunctivitis, corneal ulceration) that may reflect direct effect on the corneal epithelium or indirect effects through the associated glands and appendages (cicatricial ectropion, meibomitis, dry eye).

Visual side effects occur in approximately 60% of patients taking crizotinib.[207] These typically represented mild image persistence or photopsia within a few days of drug intake, described as trailing lights particularly during accommodation in low light conditions. These are self-limiting and do not require specific intervention. Visual changes, such as blurred vision or delayed light/dark adaptation are also commonly reported symptoms for some HSP90 inhibitors such as AUY922 and 17DMAG.[208-210] Preclinical investigation revealed that high retinal/plasma concentration ratio along with slow elimination rate of implicated agents induced photoreceptor cell death in rats, likely accounting for clinical manifestations in patients, whereas HSP90 inhibitors with very low rate of drug-related visual symptoms, such as ganetespib, had rapid retinal elimination and low retinal/plasma ratio.

Constitutional

Weight loss, with or without anorexia or other GI symptoms such as diarrhea, is commonly seen in patients treated with various novel agents and is independent of disease progression.[211] It has been shown that this may be related to drug-induced sarcopenia, as demonstrated with sorafenib.[129] Various interventions have been tested, such as use of anti-inflammatory agents, but remain without proven efficacy in preventing cancer cachexia of which weight loss is but one of the components.[212] A randomized phase 3 study in cancer patients evaluating the effect of a 4-month treatment using a progestational agent, eicosapentaenoic acid (2.2 g/day), L-carnitine (4 g/day), thalidomide (200 mg/day), or a combination of all 4 agents demonstrated that the combination regimen was well tolerated and met the primary endpoints of improved lean body mass, decreased fatigue, and resting energy expenditure while also increasing appetite compared to the other treatment arms.[213] However, whether all 4 components are needed is unclear. Anabolic agents, such as selective androgen receptor modulators, are in clinical trials for the prevention or treatment of cancer cachexia. In contrast, weight gain had been seen in some patients enrolled in first-generation MEK inhibitor trials. Although this could have been related to edema generally reported with MEK inhibitors, weight gain was determined at least for selumetinib to be due to increase in skeletal muscle mass.[214]

Immunologic

Reversal of the suppressive effect on the immune response by T cells via the blockade of the cytotoxic T-lymphocyte—associated antigen 4 or PD-1 pathway, exemplified by ipilimumab or BMS-936558, leads to increased T-cell activation and with this, immune-related adverse effects are anticipated. The presentation shares similarities with graft-versus-host disease seen in hematopoietic transplant patients, with enterocolitis and cutaneous manifestations constituting the most frequently observed adverse effects. Autoimmune manifestations can affect essentially any organ system: endocrinopathies (autoimmune thyroiditis or autoimmune hypophysitis marked by hypothyroidism, adrenal insufficiency and hypogonadotropic hypogonadism due to pan-pituitary failure), anemia, hepatitis, nephritis, pneumonitis, CNS effects (neuropathy, meningitis), ocular effects (uveitis, episcleritis, iritis), and cardiac effects (pericarditis, myocarditis) have been described. Surveillance of liver function and thyroid function with regular testing should be performed. Management approaches typically include high-dose glucocorticoids, whereas permanent discontinuation of the agents is recommended for severe toxicities. In contrast, the autoimmune effects associated with alemtuzumab are mostly

antibody-mediated syndromes such as autoimmune anemia, thrombocytopenia and neutropenia, Graves' disease, Guillain-Barre syndrome, chronic inflammatory demyelinating polyradiculoneuropathy, arthritis, and vasculitides such as Goodpasture syndrome. The mechanism proposed is the loss of self-tolerance upon immune reconstitution following the treatment-induced profound lymphopenia.[215]

Modestly increased rates of infections, such as upper respiratory tract or urinary tract infections, are seen across different targeted therapies, particularly when used in combination with chemotherapy. Bortezomib therapy was associated with a higher incidence of varicella zoster virus reactivation and development of herpes zoster compared to dexamethasone treatment (13% versus 5%).[216] This may be related to altered NF-kB signaling in mononuclear cells. Prophylactic antiviral therapy results in fewer zoster cases than no prophylaxis (3% versus 17%) in the randomized study of bortezomib with melphalan and prednisone.[217] Ruxolitinib is also associated with an approximately 2-fold higher incidence of herpes zoster (1.9%) compared with placebo treatment (0.7%) among patients with myelofibrosis.[218] This is likely related to alteration of the JAK-STAT pathway in mononuclear cells which affects T-cell immune surveillance. There is also a somewhat higher incidence of zoster among patients treated with lenalidomide with dexamethasone compared to dexamethasone alone.[219] Of note, all these agents cause some degree of lymphopenia, which may contribute to this increased risk. Patients should be advised about early signs and symptoms so that prompt treatment can be instituted.

Notwithstanding the known immunomodulatory effect induced by thalidomide and its analogues on TNF-α and other cytokines (IL-1, Il-6, IL-12),[220] altered T-cell responses have been proposed as the mechanism behind a constellation of toxicities such as autoimmune hemolytic anemias, myocarditis, pneumonitis, and dermatitis.[221] Moreover, although these agents are known to cause dose-dependent myelosuppression, changes in cytokine levels are thought to contribute to drug-induced thrombocytosis, eosinophilia, and basophilia observed during treatment with these agents in patients with myelofibrosis.[222,223] Increased incidence of second primary malignancies has also been observed with lenalidomide/dexamethasone therapy in multiple myeloma patients compared to placebo/dexamethasone (7% to 8% versus 2% to 3%), largely in the context of prior melphalan exposure, and with prolonged maintenance treatment.[224,225] Nonetheless, the mechanism is unclear and optimal prevention is subject to further investigation.

The variable risk of infusion-related hypersensitivity reactions associated with monoclonal antibodies (mAbs) is in part related to the extent of their murine residue content. Thus, murine ("-momabs") or chimeric mAbs ("-ximabs" > 50% human sequence) carry the highest risk compared with humanized mAbs ("-zumabs" up to 95% human sequence) and fully humanized ("-mumabs" 100% human sequence) mAbs. Premedication with acetaminophen and antihistamines is typically not necessary for the majority of humanized and fully human mAbs. This infusion reaction is generally a nonallergic, cytokine-mediated process that manifests within the first few hours during the first or second infusion. These reactions abate with subsequent dosing and are typically managed during the acute phase by interruption of drug infusion and administration of medications such as antihistamines and corticosteroids. In more severe cases, the use of additional supportive measures, such as oxygen, intravenous fluids, bronchodilators, and vasopressors, are indicated. A slower rate of infusion, ie, half of the initial rate, during "rechallenge" of the drug upon resolution of mild to moderate reactions can be undertaken and is usually successful. Rechallenge is not recommended for patients who experience a severe anaphylactic reaction. An IgE-mediated mechanism has been described with cetuximab. The frequency of infusion reactions is significantly higher among patients with detectable pretreatment circulating anti-cetuximab IgE.[226] This may account for the geographic differences in the incidence of infusion reactions to cetuximab (22% in Tennessee and North Carolina compared with the national average of 3%), because variations in baseline IgE levels geographically correlate with the frequency of infusion reactions.[226,227] Premedication maybe safely omitted if patients do not develop any hypersensitivity reaction during the first 2 infusions in areas with low prevalence of pretreatment cetuximab IgE antibodies.

Conclusions

A summary of reported frequencies of important adverse effects is presented in Supplemental Table 1 to facilitate comparison of data submitted to FDA in registration studies across different agents, bearing in mind that inherent differences may arise not due to the agent/drug class itself but due to the type of patient population involved. Beyond the morbidity posed by the mechanism-based toxicities, it must be recognized that a number of these "on-target" side effects, such as skin rash and hypertension, have been correlated with drug efficacy because these toxicities are an imperfect surrogate for the achievement of therapeutic drug levels. Surveillance and early management, including prevention regimens, are key to minimizing drug interruptions for severe toxicities. This is important not merely to ensure therapeutic efficacy but also to avoid emergence of symptomatic disease flares upon drug withdrawal. This disease flare phenomenon has been reported for EGFR TKIs, VEGFR TKIs, crizotinib, and ruxolitinib. These disease flares have been described typically in the context of drug discontinuation upon disease progression due to acquired resistance but also has been reported when drug is interrupted for other

unavoidable reasons, such as prior to surgery to minimize risk of poor wound healing with inhibitors of the VEGF pathway.[228-232]

In addition, the importance of understanding the pharmacology of each agent cannot be overstated. For example, because lenalidomide undergoes renal excretion predominantly, presence of renal dysfunction is associated with a greater degree of myelosuppression and doses should be adjusted appropriately for renal dysfunction. Many oral agents have pH-dependent solubility, with solubility generally decreasing at higher pH. Hence, use of proton-pump inhibitors or H2 antagonists can result in reduced absorption and effective serum concentration for erlotinib/gefitinib, ABL inhibitors (except imatinib), crizotinib, and vismodegib. Attention to other concomitant medications is also important, particularly as many of these targeted agents are CYP3A4 substrates and have relevant drug interactions that can aggravate toxicities or reduce efficacy (eg, increased risk of regorafenib-induced HFSR toxicity with grapefruit products due to CYP3A4 inhibition). Drug–food interactions also vary across agents and are similarly relevant. Table 3 summarizes relevant food and drug interactions. Lack of adherence to recommended food and drug administration can potentially decrease therapeutic efficacy (eg, reduced bosutinib concentration if taken in the fasting state) or increase toxicity (eg, increased nilotinib concentration and risk of QT prolongation if administered with food). Although various studies have related interpatient variability with regards to drug-specific toxicities (eg, UGT1A1, UGT1A9 single-nucleotide polymorphisms [SNPs] with sorafenib-induced diarrhea or hyperbilirubinemia; FLT3 SNPs with sunitinib myelosuppression; CA dinucleotide repeats in intron 1 of EGFR with skin toxicity, VEGF SNPs with bevacizumab-induced hypertension),[233-236] these findings are yet to be consistently validated or replicated, mostly because of the large sample sizes that are required.[235,236] This is an ongoing challenge facing clinical research investigating pharmacogenetically-guided drug administration.

Notwithstanding the "targeted therapy" label, these agents give rise to unanticipated toxicities despite rigorous preclinical testing, due to previously unknown mechanisms and/or the multiplicity of affected off-target proteins. These may contribute to greater toxicity when parallel pathways are simultaneously inhibited, as seen with the combinations of mTOR inhibitors with multikinase VEGF pathway or inhibitors of the PI3K pathway with MAPK pathway inhibitors.[237-239] It is thus hoped that with the availability of multiple databases and advanced computing technologies, bioinformatics-based models can present innovative in silico approaches to predicting adverse effects, in identifying and under-standing new targets as well as drug interactions to efficiently identify rare or unexpected treatment-related adverse effects that may arise during drug development of targeted agents in the near future.[240-242] ■

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