

Adverse Events to Nontargeted and Targeted Chemotherapeutic Agents

Emphasis on Hypersensitivity Responses



Brian A. Baldo, PhD^{a,b,*}, Mauro Pagani, MD^c

KEYWORDS

- Cancer drug hypersensitivities • Chemotherapeutic drug hypersensitivities
- Adverse events to cancer drugs • Monoclonal antibody adverse events
- Side effects of chemotherapeutic drugs • Monoclonal antibody hypersensitivities
- Diagnosis of chemotherapeutic drug hypersensitivities
- Desensitization to cancer drugs

KEY POINTS

- Nontargeted therapies can induce hypersensitivity reactions, some severe, in about 5% of treated patients.
- Hypersensitivity reactions are unpredictable, and it is not possible to identify patients at risk of developing such reactions.
- Diagnosis of these reactions is essential because the antineoplastic agents are, for the patients, often unique and irreplaceable.
- Prevention of hypersensitivity reactions is based on skin testing, premedication, and/or desensitization.
- Targeted therapies induce their own unique adverse effects: a lengthened QT interval, decreased left ventricular ejection fraction, and a distinct hand-foot skin reaction.
- Mucocutaneous reactions to epidermal growth factor receptor inhibitors include a papulopustular rash, xerosis, pigmentary changes, fissures, and paronychia.
- Diagnosis of hypersensitivities to small-molecule targeted therapies is hampered by a lack of suitable tests and/or their availability. Few desensitization protocols have been used so far.

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^a Molecular Immunology Unit, Kolling Institute of Medical Research, Royal North Shore Hospital of Sydney, Sydney 2065, Australia; ^b Department of Medicine, University of Sydney, Sydney 2006, Australia; ^c Medicine Department, Pieve di Coriano Hospital, Azienda Ospedaliera C.Poma, Mantova, Italy

* Corresponding author. 11 Bent Street, Lindfield, New South Wales 2070, Australia.

E-mail address: babaldo@iinet.net.au

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Continued

- Monoclonal antibodies provoke all 4 types of hypersensitivities, including immune cytopenias, vasculitis, serum sickness, and pulmonary and cardiac events. Some successful desensitization protocols have been developed.

INTRODUCTION

The so-called chemotherapeutic drugs cause a wide variety of adverse events ranging from, for example, headache, mild gastrointestinal symptoms, cough, transient rash, and itching to severe cytopenias; anaphylaxis; lung, liver, cardiac, and neural toxicities; several reactions of the skin and mucous membranes; and rarely life-threatening bullous toxidermias.¹⁻³ Although only some of these myriad adverse reactions are true hypersensitivities, that is, reactions with a specific humoral and/or cellular immune component or basis, reactions are sometimes incorrectly described as hypersensitivities, whereas other true hypersensitivities go unrecognized.^{1,3,4} Although the term *hypersensitivity* is widely used in immunology, allergy, and oncology and features prominently in reports of clinical trials, information released by regulatory agencies and pharmaceutical companies, a common definition of the term is frequently lacking across the disciplines. The word is often applied to reactions that clearly have no immune basis or when the underlying mechanism has not been established.³ Now, with a rapidly growing number of drugs (already well in excess of 100) used for treatment of the numerous different cancers,⁵ neglect by allergists and immunologists of the wide range of drug-induced adverse systemic and cutaneous reactions provoked by these agents needs to be recognized and remedied both at the levels of diagnosis and management.

Here the authors attempt to bring the problem of drug-induced adverse events so commonly seen during cancer therapy to the attention of allergists by outlining the extent, variety, and nature of reactions that may occur; classifying the drugs to permit understanding of the relationships and differences between them and the responses they provoke; highlighting the mechanistic basis of true drug-induced hypersensitivities while emphasizing the need for the acceptance of a common definition across all disciplines; and discussing the need for premedication treatments, desensitizations, and specialized diagnostic testing to identify the 4 types of hypersensitivities. In an attempt to logically organize for classification and presentation the large number and diverse nature of the small-molecule antineoplastic drugs, monoclonal antibodies (mAbs) and cytotoxic chimeric proteins, the different agents are firstly divided on a nontargeted and targeted basis and then considered as some individual examples from groups classified according to their mechanisms of action.^{3,6,7}

NONTARGETED DRUGS

Hypersensitivity reactions to chemotherapeutic drugs have been documented for most cancer chemotherapies. They are considered to be uncommon, even though their real incidences are not well known.⁸ In fact, most reactions are usually mild and are not reported by oncologists, so the problem is probably underestimated. However, hypersensitivity reactions represent a significant problem with certain agents, in particular platinum compounds, taxanes, *L*-asparaginase, epipodophylotoxins, and procarbazine, whereas it is lower with others.⁹ In this regard, chemotherapeutic agents may be divided into 3 groups represented by drugs with high, intermediate, or low potential to cause hypersensitivity reactions (**Table 1**). Reactions

Table 1
Chemotherapeutic drugs divided on the basis of their potential to cause hypersensitivity reactions

Drugs with High Potential	Drugs with Low Potential	Drugs with Occasional Potential
L-Asparaginase (<i>Escherichia coli</i> -derived, <i>Erwinia</i> -derived, pegasparaginase)	Anthracyclines (daunorubicin, doxorubicin, epirubicin, mitoxantrone, idarubicin, valrubicin)	Bleomycin
Platinum compounds (carboplatin, cisplatin, oxaliplatin)	Mercaptopurine	Cyclophosphamide
Taxanes (paclitaxel, docetaxel)	Azathioprine	Vincristine
Epipodophyllotoxins (etoposide, teniposide)		Methotrexate
Procarbazine		Mitomycin C

can be caused by the parent compounds, their metabolites, or the solvent in which they are solubilized (eg, Cremophor EL [a polyethoxylated castor oil] for paclitaxel).

Risk Factors

Knowledge of the risk factors for the development of a hypersensitivity reaction to a chemotherapeutic drug is essential for the identification of at-risk patients. Risk factors, described by several researchers, include previous exposure, a personal history of allergies, route of administration, the preparation/additives of the drug, coincident medications, and concurrent autoimmune diseases¹⁰; but risks have been defined for only a few drugs, for example, a previous exposure to platinum salts¹¹ and intravenous administration for L-asparaginase.¹² **Table 2** summarizes the most relevant published studies of risk factors.

Table 2
Risk factors for hypersensitivity reactions to chemotherapy

No of Patients	Culprit Drug	Risk Factors	Author
	L-Asparaginase	Intravenous administration	Weiss, ¹² 1992
15	Paclitaxel	History of bee-sting HSRs	Grosen et al, ¹³ 2000
83	Carboplatin	History of HSRs to drugs	Markman et al, ¹⁴ 2003
14	Paclitaxel	History of skin HSRs to drugs, obesity, postmenopausal status	Sendo et al, ¹⁵ 2005
68	Carboplatin	Carbo-free interval >12 mo History of HSRs to drugs	Schwartz et al, ¹⁶ 2007
15	Carboplatin	Carbo-free interval >23 mo History of HSRs	Gadducci et al, ¹¹ 2008
45	Oxaliplatin	OHP-free interval >12 mo, age <60 y	Mori et al, ¹⁷ 2010
166	Carboplatin + paclitaxel	Age <70 y	Joly et al, ¹⁸ 2011
102	Docetaxel	Second line of chemotherapy	Syrigou et al, ¹⁹ 2011
22	Carboplatin + paclitaxel	History of systemic HSRs	Piovano et al, ²⁰ 2012

Abbreviations: Carbo, carboplatin; HSRs, hypersensitivity reactions; OHP, oxaliplatin.

Clinical Pictures

Clinical manifestations are variable, and reactions are unpredictable. The symptoms involve the skin (rash, pruritus, urticaria, angioedema, palmar erythema, facial flushing), gastrointestinal tract (abdominal pain, nausea, diarrhea), respiratory tract (dyspnea, bronchospasm), and the system (alterations in blood pressure and heart rate). More severe reactions (always occurring during the infusion of chemotherapy) provoke chest pain; angina pectoris; anaphylaxis; and, in rare cases, even death.¹⁰ Mild to moderate reactions can develop either during the treatment or in the 24 to 72 hours after the end of the administration of chemotherapy.

Pathogenesis

The mechanisms of the hypersensitivity reactions are not always intensively analyzed. Similar to other drug reactions and considering the results of some skin tests and in vitro analyses, the more severe acute reactions probably involve drug-specific immunoglobulin E (IgE) antibodies (eg, with the platinum compounds). Most mild reactions seem to be determined by other mechanisms, such as direct mast cell or basophil activation/degranulation or activation of the complement cascade.²¹ In addition, cases of type II, III, or IV hypersensitivity reactions have been reported. **Table 3** shows examples of these 4 types of reactions.

Diagnosis

The correct identification and diagnosis of hypersensitivity reactions to cytostatic drugs play a crucial role in the treatment of neoplastic patients because, unlike other drugs (eg, antibiotics) that may be easily replaced and exchanged in case of adverse reactions, chemotherapeutic drugs are often uniquely complementary for a particular cancer and, therefore, essential for the treatment of the disease (**Box 1**). Therefore, if a hypersensitivity reaction occurs, the physician may have to decide between the benefit of continuing the treatment and the risk of, for example, a potential fatal anaphylactic reaction during the subsequent chemotherapy. Hence, the correct diagnosis of an allergic side effect to a cytostatic drug is crucial and cannot be postponed.

The diagnosis of hypersensitivity reactions to a drug is based on history, clinical manifestations, and if possible, skin tests, in vitro tests and provocation tests.²² In neoplastic patients, anamnestic evaluation is complicated by many confounding factors: (1) patients often take a lot of drugs, for example, analgesics or antiemetics that may also provoke hypersensitivity reactions; (2) the neoplastic cells may cause, probably via the direct activation of mast cells, some clinical manifestations that mimic

Table 3 Immunopathogenetic mechanisms of hypersensitivity reactions			
Type of HSR	Immunopathogenetic Mechanism	Symptoms	Example
I	IgE-mediated	Urticaria, angioedema, bronchospasm, anaphylaxis	L-asparaginase Platinum salts?
II	Cytolytic antibodies (IgG or IgM)	Hemolytic anemia	Oxaliplatin
III	Antigen-antibody immune complex	Vasculitis	Methotrexate
IV	Cell-mediated sensitized T lymphocytes	Contact dermatitis	Anthracyclines

Abbreviation: HSR, hypersensitivity reaction.

Box 1**Difficulties in the diagnosis of hypersensitivity reactions to chemotherapy**

Anamnesis: Neoplastic patients take many drugs that can each provoke reactions, and some cancers increase the risk of allergic manifestations.

Skin tests: Skin tests are only useful for platinum salts. Their role for other drugs (L-asparaginase, paclitaxel, etoposide, procarbazine, cyclophosphamide, and so forth) is uncertain.

In vitro tests: Detection of drug-specific IgE is probably useful in cases of suspected hypersensitivity reactions to platinum salts. There are very little data for other classes of drugs.

hypersensitivity reactions; and (3) some epidemiologic studies have demonstrated that certain cancers are associated with an increased risk of allergies.^{23,24} Therefore, the physician must obtain a careful clinical history, analyzing the characteristics and chronology of symptoms and their relationship to the intake of cytotoxic agents or other drugs. For example, hypersensitivity reactions to taxanes usually develop during the first or second infusion, whereas reactions to platinum salts occur after several doses of therapy, on average 6 to 7, suggesting that desensitization to the drug is needed.

The clinical history is also important because chemotherapy may often provoke non-IgE-mediated reactions and even non-immune-mediated reactions.¹⁰ In the presumed immune-mediated reactions, prick and intradermal tests performed to detect drug-specific IgE are only useful for a few chemotherapeutic drugs, in particular platinum salts, but not for other drugs. The role of platinum drug-specific IgE antibodies in the development of hypersensitivity reactions to these agents, especially carboplatin and oxaliplatin, is well documented^{10,25}; the finding of positive skin tests underlines an IgE-mediated mechanism. Indeed, skin tests are rather sensitive for the diagnosis of hypersensitivity reactions to platinum compounds with a sensitivity ranging from 75% to 100%.²⁵⁻³¹ The most reliable results are obtained with the intradermal test when reactions have developed during the infusion of the drug or within 2 hours of the end of therapy.²⁵ However, Madrigal-Burgaleta and colleagues³² observed positive prick tests in 4 patients with well-documented hypersensitivity reactions to oxaliplatin. The patch test, helpful in the diagnosis of delayed reactions, does not seem to be useful in the diagnosis of allergies to cytostatic drugs.²⁵ In addition, some recent preliminary observations demonstrated the presence of specific IgE for carboplatin and oxaliplatin in the serum of allergic patients.^{32,33} For other chemotherapeutic drugs, skin tests proved positive in some patients who reacted to paclitaxel,³⁴ cyclophosphamide,^{35,36} L-asparaginase,³⁷ procarbazine,³⁸ and etoposide^{39,40}; but the diagnostic and predictive value of these results remains uncertain. **Table 4** summarizes the concentrations of chemotherapeutic drugs used for skin testing. Apropos

Table 4**Recommended skin test concentrations for chemotherapeutic drugs**

Drug	SPT	IDT	Comments
Carboplatin	10 mg/mL	1.0 mg/mL	—
Oxaliplatin	1 mg/mL	0.1 mg/mL	—
Cisplatin	1 mg/mL	0.1 mg/mL	—
Other drugs	Undiluted	1:10 dilution	Not all chemotherapeutic drugs have been tested

Abbreviations: IDT, intradermal test; SPT, skin prick test.

of this, some antineoplastic agents, namely, anthracyclines, vinblastine, vincristine, mitomycin C, and mechlorethamine, can determine severe local cutaneous reactions when accidentally touch the skin; therefore, skin tests should not be performed with these drugs.

Factors Influencing the Treatment in Case of Hypersensitivity Reactions

After an allergological work-up during which a severe hypersensitivity reaction to a chemotherapeutic drug is diagnosed, the oncologist and/or allergist must decide whether to stop the chemotherapy or continue it with the same drug or a substitute drug. The decision should be taken after carefully analyzing the factors related to the severity of the reaction, the characteristics of the patient, the type and stage of the disease, and the nature and details of the chemotherapy.

The National Cancer Institute has graded the severity of the reactions into 5 levels (Table 5).⁴¹ Generally, grade 1 to 2 reactions allow the continuation of chemotherapy without modification. Grade 3 reactions may require the substitution of the culprit drug. If this is not possible, and there is robust evidence of efficacy, premedication with steroids and antihistamines and/or a reduction in the rate of infusion are recommended. In the case of grade 4 reactions, rechallenge should be avoided and the drug replaced, unless the treatment is curative. The application of a desensitization protocol should also be evaluated (Box 2).

Regarding the factors related to the disease and patients, the level of cancer progression, a poor performance status, important comorbidities, or the use of certain drugs (eg, beta-blockers for immediate hypersensitivity reactions) are relevant and may be important contraindications for the infusion of the culprit drug.

Regarding chemotherapy, the physician must evaluate if it is possible to replace the culprit drug with another belonging to a different class of cytostatic drugs or with another drug of the same class. For example, substitution of carboplatin with

Table 5 Grading of hypersensitivity reactions according to National Cancer Institute's Criteria	
Grade	Hypersensitivity Reactions
1	Transient flushing or rash Drug fever 38°C (100.4°F) Intervention not indicated
2	Rash, flushing, urticaria, dyspnea, Drug fever 38°C (100.4°F) Intervention or infusion interruption indicated, responds promptly to symptomatic treatment (eg, antihistamines, nonsteroidal antiinflammatory drugs, narcotics), prophylactic medications indicated <24 h
3	Symptomatic bronchospasm with or without urticaria, allergy-related edema/ angioedema, hypotension Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion), recurrence of symptoms following initial improvement, hospitalization indicated for clinical sequelae (eg, renal impairment, pulmonary infiltrates)
4	Anaphylaxis Life-threatening consequences, urgent intervention indicated
5	Death

Data from National Cancer Institute. Common Terminology Criteria for Adverse Events v4.03 (CTCAE). 2009. Available at: <http://ctep.cancer.gov>. Accessed October 30, 2013.

Box 2**Recommendations in case of hypersensitivity reactions to chemotherapy**

Grade 1 to 2 reactions allow the continuation/pursuit of drug therapy without modification.

Grade 3 reactions may require the substitution of the culprit drug. If this is not possible and when there is a robust evidence of efficacy, premedication with steroids and antihistamines and/or reduction of the rate of infusion is recommended.

In case of *grade 4* reactions, rechallenge should be avoided and the drug replaced, unless the treatment is curative; in this case, the application of a desensitization protocol should be evaluated.

another platinum compound, cisplatin, may be limited (and guided) by cross-reactivity of the platinum-specific IgE antibodies.⁴² Leguy-Seguin and colleagues²⁵ observed positive skin tests to oxaliplatin and carboplatin in 3 patients allergic to oxaliplatin and who had never been exposed to carboplatin. However, 8 allergic patients tolerated another platinum compound, which was skin test negative.²⁵ Thus, if skin tests are negative with another platinum agent, the alternative drug might be used.^{25,43,44} For some drugs belonging to the same class (eg, the taxanes), which share the same therapeutic indications but may cross-react, docetaxel could potentially substitute for paclitaxel in cases of severe hypersensitivity reactions to the latter. For example, Lokich and Anderson⁴⁵ and Moon and colleagues⁴⁶ obtained good results on 6 patients; but Dizon and colleagues⁴⁷ and Sanchez-Munoz and colleagues⁴⁸ reported a cross-reactivity rate of 90% and 41%, respectively, for the 2 drugs, presumably because of their structural similarity. Generally, therefore, the substitution of one taxane by another is not recommended. In the case of hypersensitivity reactions to *Escherichia coli*-derived *L*-asparaginase, its substitution with the *Erwinia*-derived preparation or, better still, the pegylated (PEG) form, PEG-asparaginase, is usually safe, although about 15% of patients may develop allergic reactions to pegasparaginase.^{49,50} Unfortunately, the availability of *Erwinia*-derived *L*-asparaginase and pegasparaginase is limited in many parts of the world, making premedication or desensitization protocols necessary alternatives. Following premedication with steroids and antihistamines and a desensitization protocol on 16 patients with previous allergic reactions to *L*-asparaginase, Soyer and colleagues⁵¹ showed that chemotherapy could be completed in almost 70% of the patients. Hence, in countries with shortages of alternative asparaginase preparations, this approach might be a suitable option.

Prevention of Hypersensitivity Reactions to Nontargeted Drugs

To prevent allergic reactions, 3 possibilities are available: premedication, skin testing, and desensitization (**Box 3**).

Premedication with steroids and antihistamines, used worldwide in the schedules of chemotherapy with taxanes, has dramatically decreased the incidence of hypersensitivity reactions to 2% to 4% of cases.^{12,21,52} Recent findings by Berger and colleagues⁵³ demonstrated that premedication was not mandatory after 2 doses of paclitaxel if patients did not previously develop hypersensitivity reactions. This observation is undoubtedly interesting, but more studies are necessary to confirm the results.

Another modality of treatment emerged from the clinical trials of Olson and colleagues⁵⁴ and Markman and colleagues.⁵⁵ Both groups of researchers readministered paclitaxel to patients who experienced hypersensitivity reactions to the drug on the same day the reaction occurred: 93% of the patients were able to complete the

Box 3**Procedures for the prevention of hypersensitivity reactions to chemotherapy**

1. *Premedication* with steroids and antihistamines is indicated in case of administration of taxanes, whereas it is not useful to prevent hypersensitivity reactions caused by platinum salts.
2. *Skin tests* (prick and intradermal) play an important role in the prevention of reactions to platinum salts. They are especially effective for patients who are less than 70 years of age who received at least 4 doses of platinum salt and when the interval before readministration is greater than 12 months. Preventive skin tests are not indicated for other classes of chemotherapy.
3. *Desensitization* must be performed in cases of severe hypersensitivity reactions to a chemotherapeutic drug when the drug is irreplaceable and the therapy cannot be discontinued. Desensitization can be used for all drugs, but the widest experiences are with platinum compounds and the taxanes.

planned chemotherapy without reactions. The mechanism postulated by the researchers is that the first reactions depleted the mediators responsible for the symptoms. Premedication is said to be effective and has been recommended for the prevention of hypersensitivity reactions to pegasparaginase in adult patients,⁵⁶ but several researchers have observed that premedication is ineffective in preventing true IgE-mediated allergic reactions to platinum salts.^{42,57–59}

Skin tests in between chemotherapy courses to predict a reaction have been analyzed for carboplatin and oxaliplatin. Markman and colleagues⁶⁰ demonstrated that intradermal tests with an undiluted solution of carboplatin (0.02 mL) performed 30 minutes before the chemotherapy were able to identify patients who could receive carboplatin safely with a negative predictive value of 98.5%. In addition, in a recent study,⁶¹ 101 patients were submitted to skin testing with oxaliplatin. Two patients proved positive, whereas 5 developed hypersensitivity reactions despite a negative skin test finding (false-negative rate 5.05%). These patients underwent desensitization, and the planned schedule of chemotherapy was completed in 5 cases. Therefore, skin tests for carboplatin and oxaliplatin seem to be useful for the primary prevention of an allergic reaction to these drugs. They could be performed on patients after 5 cycles of chemotherapy containing carboplatin, especially when the therapy is readministered to neoplastic patients after an interval between the last and the new infusion of more than 12 months.

Desensitization is indicated for neoplastic patients who experience severe allergic reactions despite premedication, when the culprit drug is not replaceable, and/or in cases of positive skin tests to platinum compounds.⁶⁰ The aim of desensitization is to induce a transient tolerance that can be achieved in a relatively short period (on average 6 hours), permitting the safe reintroduction of a drug that provoked the hypersensitivity reactions.⁶² In chemotherapy, most desensitization protocols involve platinum compounds or taxanes; but, theoretically, desensitizations to other cytostatic drugs could be attempted and might be successful with this procedure.^{63,64} Clinical experience shows that desensitization is effective in IgE- and non-IgE-mediated immediate hypersensitivity reactions of any severity.³¹ Many protocols have been described in the scientific literature, but the best evaluated one seems to be a 12-step procedure developed by Castells and colleagues²⁷ in which the patients receive the established dose for chemotherapy divided into 12 incremental steps. In brief, the drug is prepared in 3 solutions: the first contains a 100-fold dilution of the final target concentration; the second contains a 10-fold dilution; and the third is obtained

by subtracting from the final total dose the cumulative dose presented in the first 2 solutions. Each solution is administered in 4 steps at increasing infusion rates. This protocol usually provokes adverse reactions, especially during the infusion of the third solution; but a temporary stop of the therapy and the parenteral administration of antihistamines and steroids usually permits the continuation of the therapy until completion. In a recent work, Patil and colleagues⁶⁵ identified 3 different groups of patients with hypersensitivity reactions, namely, skin test positive, skin test negative, and skin tests converters, in which skin test results converted to positive during desensitization after an initial negative result. Skin test–positive patients and converters were more likely to have hypersensitivity reactions during desensitization, whereas true-negative patients could subsequently complete the planned schedule of chemotherapy without desensitization. Desensitization is an effective and safe procedure; but it is also rather complex, involving a team of allergists, oncologists, nurses, and possibly anesthetists. Thus, it is normally used for life-saving and irreplaceable cytostatic drugs only. Lastly, desensitization protocols do not alter the effect of therapy. **Table 6** summarizes the different possible management approaches after hypersensitivity reactions to chemotherapeutic drugs.

TARGETED DRUGS

Specific targeting of tumor cells without inflicting collateral damage on normal healthy cells has been, and remains, a long-standing aim in cancer therapy. With the introduction of targeted approaches, including signal transduction therapies,⁶⁶ selected mAbs,^{6,7,67} and several other sophisticated strategies, such as employment of cytotoxic chimeric proteins^{68,69} and approaches based on an understanding of the proteasome,^{70,71} the long-awaited aim of targeted therapies is beginning to look achievable. However, although some results are encouraging, these strategies promising efficacy with minimal toxicity have, with a small number of notable exceptions, so far brought minimal success.⁶⁶ For the authors' purposes here, targeted drugs have been divided into the natural or synthetic small molecules (ie, generally molecular weight <1 kDa) almost always of nonbiologic origin and the biologicals, in particular mAbs and recombinant fusion proteins, for example, denileukin diftix⁶⁸ and aflibercept.⁶⁹

Table 6
Handling procedures after severe reactions to chemotherapy

Drug	Management After Reactions
Platinum compounds	Desensitization
Taxanes	Premedication with steroids and antihistamines
L-Asparaginase	Substitution with different preparation Premedication with steroids or antihistamines Desensitization
Procarbazine	Discontinue
Epipodophyllotoxins	Premedication with antihistamines Slow infusion rate
Anthracyclines	Slow infusion rate Desensitization
Mercaptopurine, azathioprine	Desensitization
Methotrexate	Premedication with steroids or antihistamines Desensitization
Cytarabine	Discontinue
Cyclophosphamide and ifosfamide	Discontinue

Small Chemotherapeutic Drugs

The first example of using an understanding of the signaling network to design and employ targeted drugs was the application of the estrogen receptor antagonist tamoxifen for the treatment of some estrogen-dependent breast cancers.⁷² Signal transduction therapy involves the identification of signaling molecules, such as hormones, ATP, growth factors, neurotransmitters, cytokines, and chemokines, and their altered pathways and consequent cell responses like cell division, gene expression, metabolic changes, and apoptosis.⁶⁶ The principle of signal transduction therapy is summarized in Fig. 1; some examples of differently targeted chemotherapeutic antineoplastic drugs are set out in Table 7, which also shows the structures, cancer indications, and mechanisms of action of the selected drugs (see reviews^{3,88}). Protein kinases in particular, either in receptor or nonreceptor form, have been used as targets for a new generation of antitumor drugs. For example, the oncogene BCR-ABL (fusion of the breakpoint cluster region [BCR] gene on chromosome 22 and the ABL tyrosine kinase gene on chromosome 9) mutation formed by the so-called Philadelphia translocation⁸⁹ is present in most patients with chronic myeloid leukemia (CML); its fusion protein Bcr-Abl, essential in the induction of leukemia, is expressed in high levels. CML cells are absolutely dependent (ie, show oncogene addiction) on Bcr-Abl kinase activity, a dependence exploited by the drug imatinib (Gleevec), which inhibits the enzyme and has been successful in the treatment of the leukemia.⁸⁹ Dasatinib (Sprycel) is another protein tyrosine kinase inhibitor that shows a broader spectrum of enzyme activity blocking Bcr-Abl, Src, and other tyrosine kinases.⁸⁹ Gefitinib (Iressa)

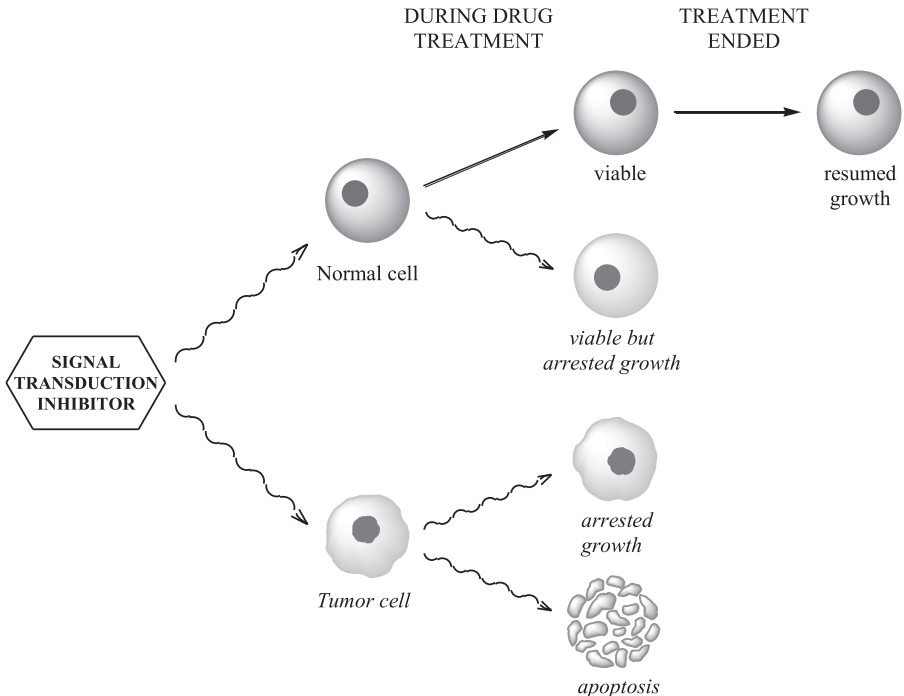
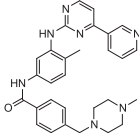
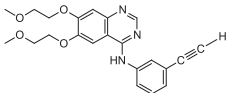
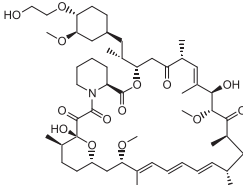
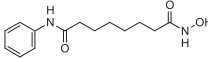


Fig. 1. Simplified representation of the principle of signal transduction therapy for cancers. (Adapted from Baldo BA, Pham NH. Adverse reactions to targeted and non-targeted chemotherapeutic drugs with emphasis on hypersensitivity responses and the invasive metastatic switch. *Cancer Metastasis Rev* 2013;32:737; with permission.)

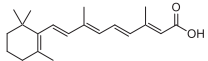
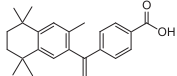
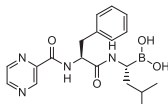
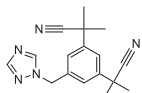
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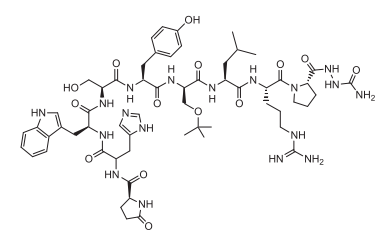
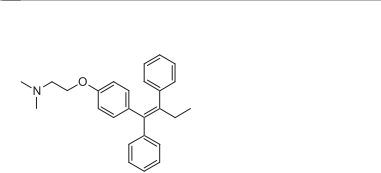
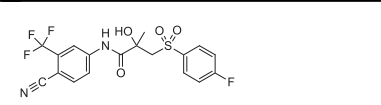
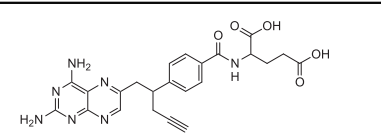
Detailed examples of differently targeted chemotherapeutic drugs^a and their hypersensitivity/adverse reactions

Generic and Trade Name and Classification ^b on Basis of Mechanism		Structure	Cancer Indications	Mechanisms of Action ^b	Hypersensitivity ^c /Adverse ^d Reactions	References ^e
SIGNAL TRANSDUCTION INHIBITORS						
Nonreceptor tyrosine kinase inhibitors ^f Imatinib (Gleevec)			Ph+CML, Ph+ALL, GIST	Blocks Bcr-Abl tyrosine kinase from phosphorylating	<i>Systemic:</i> cytopenias, hypersens pneum, hepatotox, tIs, CV, GI <i>Cutaneous:</i> pr, ppr, vasc, hyperpig, agep, SJS, em	^{73,74}
Receptor tyrosine kinase inhibitors ^g Erlotinib (Tarceva)			NSCL, pancreatic	EGFR inhibitor, binds ATP receptor site and interrupts signal cascade	<i>Systemic:</i> cytopenias, hepatotox, ild, renal and ocular disorders <i>Cutaneous:</i> ppr, pr, xerosis, hyperpig, hfsr, digital fissures, paronychia	⁷⁵
mTOR ser/threo kinase inhibitors ^h Everolimus (Afinitor)			Breast, RCC, PNET, SEGA	Binds protein FKBP12; this complex inhibits mTOR ultimately dephosphorylating S6K1 and causing apoptosis of cancer cells	<i>Systemic:</i> cytopenias, pneumonitis, renal failure, edema, oral ulcers, dyspnea, GI <i>Cutaneous:</i> acneiform rash, erythema, st, nail disorders, xerosis	⁷⁶
Histone deacetylase inhibitors ⁱ Vorinostat (Zolinza)			CTCL	Accumulation of acetylated proteins including BCL6, p53, Hsp90 ^j → growth arrest and apoptosis	<i>Systemic:</i> cytopenia, pulm embolism, thrombosis, GI <i>Cutaneous:</i> exfol dermatitis, pr, alopecia	⁷⁷

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Table 7
(continued)

Generic and Trade Name and Classification ^b on Basis of Mechanism	Structure	Cancer Indications	Mechanisms of Action ^b	Hypersensitivity ^c /Adverse ^d Reactions	References ^e
Target the PML-RAR α oncoprotein ^k Tretinoin (Vesanoid)		APL	Downregulates S100A 10 ^l and fibrinolytic activity	<i>Systemic</i> : retinoic acid syndrome, cts, retinoid toxicity, resp and ear disorders <i>Cutaneous</i> : pr, photosens, erythema, xeroderma	⁷⁸
Bind retinoid receptors Bexarotene (Targretin)		CTCL	Activates retinoid X receptors changing gene expression, decreasing cell proliferation and producing tumor regression and apoptosis	<i>Systemic</i> : lipid abnormalities, pancreatitis, anemia, leuko, hypothyroidism, edema, infections <i>Cutaneous</i> : ppr, acne, keratitis, bullous rash, corneal lesions, photosens, xerosis, alopecia	⁷⁹
PROTEASOME INHIBITORS^m					
Bortezomib (Velcade)		MM, MCL, NHL	Inhibits proteasome by binding to chymotrypsin and caspase sites, may suppress degradation of proapoptotic factors	<i>Systemic</i> : cytopenias, hypotension, cardiac disorders, ARDS, tIs, hepatic events, pneumonia, dyspnea <i>Cutaneous</i> : rash, ⁿ pr, erythema, U, facial edema, vasc, ten	⁸⁰
HORMONAL EFFECTS					
Inhibitors of hormone synthesis Anastrozole ^o (Arimidex)		Breast	Binds aromatase preventing conversion of androgens $\rightarrow$ estrogens	<i>Systemic</i> : hot flushes, arthritis, arthralgia, dyspnea, osteoporosis, hypertension <i>Cutaneous</i> : rashes, pr, mpr, erythema nodosum, lupus, vasc, em, SJS	⁸¹

GnRH^P agonists Goserelin (Zoladex)		Prostate, breast	Synth analogue of GnRH, binds GnRH receptor → increase in Gn and reduction in hormone levels	<i>Systemic:</i> hot flushes, anemia, dtdf, osteoporosis, anaphylaxis, vaginitis <i>Cutaneous:</i> rash, itch, rps, acne, seborrhea, alopecia	82
Hormone receptor antagonists Tamoxifen^a (Nolvadex)		Breast (estrogen receptor positive and postme- nopausal women)	Antagonist of estrogen receptor inhibiting breast cancer cells requiring estrogen, antiangiogenic effect	<i>Systemic:</i> hot flushes, vaginal discharge, endometriosis, interstit pneumonia, thrombosis, vision reduction <i>Cutaneous:</i> U, angio, vasc, ^r pr vulvae, em, bullous pemphigoid, SJS	83
Antiandrogens Bicalutamide (Casodex)		Prostate, assessed for ovarian and metastatic breast cancer	Binds androgen receptor preventing its activation and accelerates degradation of receptor	<i>Systemic:</i> hot flushes, thrombo, interstit pneumonia, gynecomastia <i>Cutaneous:</i> U, angio, pr, alopecia	84
TARGETED ANTIFOLATE DRUGS					
Pralatrexate (Folotylin)		PTCL	Folate analogue antimetabolite accumulates in cancer cells, which overexpress RFC-1 and interferes with DNA synth → cell death	<i>Systemic:</i> thrombo, febrile neutro, anemia, mucositis, fetal harm, pyrexia, tls <i>Cutaneous:</i> rash, pr, exfoliation, ulceration, ten	85

(continued on next page)

Table 7
(continued)

Generic and Trade Name and Classification ^b on Basis of Mechanism	Structure	Cancer Indications	Mechanisms of Action ^b	Hypersensitivity ^c /Adverse ^d Reactions	References ^e
TARGETED CYTOTOXIC CHIMERIC PROTEINS					
Denileukin diftitox (Ontak)	Diphtheria toxin–IL-2 fusion protein	CTCL	Modified diphtheria toxin released causing ADP-ribosyltransferase-mediated inhibition of protein synthesis and death	<i>Systemic:</i> infusion reaction, cls, pyrexia, vision disturbances, periph edema, dyspnea, cough, GI <i>Cutaneous:</i> pr, ten	68,86
Ziv-aflibercept (Zaltrap)	Fusion protein of IgG1 Fc and VEGFR1 and VEGFR2 ligand-binding domains	MCRC	Acts as soluble decoy VEGF receptor and angiogenesis inhibitor	<i>Systemic:</i> leuko, neutro, thrombo, GI perforation, hemorrhage, hypertension, proteinuria, venous thromboembolism <i>Cutaneous:</i> acral erythema, hyperpigm, st, compromised wound healing	69,87

Abbreviations: agep, acute generalized exanthematous pustulosis; ALL, acute lymphoblastic leukemia; angio, angioedema; APL, acute promyelocytic leukemia; ARDS, acute (adult) respiratory distress syndrome; BCL6, B cell lymphoma 6 protein; cls, capillary leak syndrome; CML, chronic myelogenous leukemia; CTCL, cutaneous T-cell lymphoma; CV, cardiovascular disorders; didf, drug-induced disease flare (tumor-flare effect); EGFR, epidermal growth factor receptor; em, erythema multiforme; exfol, exfoliative; GI, gastrointestinal adverse events; GIST, gastrointestinal stromal tumor; Gn, gonadotropin; GnRH, gonadotropin-releasing hormone; hepatotox, hepatotoxicity; hfsr, hand-foot skin reaction; Hsp90, heat shock protein 90; hyperpigm, hyperpigmentation; hypersens, hypersensitivity; ild, interstitial lung disease; interstit, interstitial; leuko, leukopenia; MCL, mantle cell lymphoma; MCRC, metastatic colorectal cancer; MM, multiple myeloma; mpr, maculopapular rash; mTOR, mechanistic (or mammalian) target of rapamycin; neutro, neutrocytopenia; NHL, non-Hodgkin lymphoma; NSCL, non-small cell lung cancer; p53, tumor protein 53; periph, peripheral; Ph+, Philadelphia chromosome positive; photosens, photosensitization; PML-RAR α , promyelocytic leukemia retinoic acid receptor α oncogene fusion protein; PNET, pancreatic neuroendocrine tumor; pneum, pneumonitis; ppr, papulopustular rash; pr, pruritus; PTCL, peripheral T cell lymphoma; pulm, pulmonary; RCC, renal cell carcinoma; RFC-1, reduced folate carrier type 1; rpcs, relapsing polychondritis cutaneous symptoms; SEGA, subependymal giant cell astrocytoma; ser/threo, serine/threonine; SJS, Stevens-Johnson syndrome; st, stomatitis; synth, synthesis; ten, toxic epidermal necrolysis; tls, tumor lysis syndrome; thrombo, thrombocytopenia; U, urticaria; vasc, vasculitis; VEGFR, vascular endothelial growth factor receptor.

^a MAbs not included (see [Table 8](#)).

^b Some drugs exert their actions by more than one mechanism and might, therefore, be classified into more than one category. The classification shown is deemed to be the most appropriate one.

^c Reactions known, or suspected, of having an immunologic basis.

^d Reactions, such as weakness, fatigue, headache, and so forth, and gastrointestinal (GI) symptoms like nausea, vomiting, diarrhea, constipation, appetite reduction, dyspepsia, and so forth, are not recorded here because they are common to so many of the drugs. Where such reactions are important, they are referred to collectively as GI.

^e For additional references for all drugs listed here see [see 3](#).

^f Other frequently used registered drugs in this group include bosutinib, crizotinib, dasatinib, nilotinib, and ponatinib.

^g Other frequently used registered drugs in this group include axitinib, gefitinib, lapatinib, pazopanib, regorafenib, sorafenib, sunitinib, and vandetanib.

^h Temsirolimus and rapamycin are also in this group.

ⁱ Romidepsin is also in this group.

^j BCL6 protein is a zinc finger transcription factor, a sequence-specific repressor of transcription. p53 (tumor protein 53), is a tumor suppressor protein that regulates the cell cycle. Hsp90, heat shock protein 90, is a molecular chaperone, assisting protein folding and stabilizing some proteins in tumor growth.

^k Arsenic trioxide, also used for acute promyelocytic leukemia, also binds to PML-RAR α .

^l A plasminogen receptor.

^m Carfilzomib is also used as a proteasome inhibitor for multiple myeloma.

ⁿ Incidence is 8% to 18%.

^o An aromatase inhibitor. Other registered aromatase inhibitors include exemestane and letrozole.

^p Other analogues include leuprolide.

^q A selective estrogen receptor modulator.

^r Nineteen percent of patients experience skin reactions.

and erlotinib (Tarceva) target the epidermal growth factor receptor (EGFR; also known as ErbB1 and HER1), a member of the ErbB family of receptors. Other receptor tyrosine kinase inhibitors are used to target growth factor receptors, including vascular endothelial growth factor receptors (VEGFRs) and platelet-derived growth factor receptors (PDGFRs). Lapatinib (Tykerb) inhibits ErbB1 and ErbB2 (human epidermal growth factor receptor 2 [HER2]); sorafenib (Nexavar) inhibits VEGFR and PDGFR; sunitinib (Sutent) inhibits VEGFR and PDGFR; and pazopanib (Votrient) targets several tyrosine kinases, including VEGFRs, PDGFRs, and fibroblast growth factor receptor 2 (FGFR2). Increased understanding of the proteasome and its role in protein degradation via the ubiquitin-proteasome pathway has led on to the development of proteasome inhibitor drugs. These drugs, such as bortezomib (Velcade), seem to bind to chymotrypsin and caspase catalytic sites in the proteasome core where degradation of proapoptotic factors leads to death of multiple myeloma and mantle lymphoma cells.^{6,70,71} Other signal transduction strategies are represented in [Table 7](#).

mAbs

Table 8 lists the 15 mAbs currently approved for cancer therapy together with the specific target and approved indications for each mAb. These mAbs are directed to a limited number of targets: 4 to the B lymphocyte antigen CD20; 3 to EGFR2 (HER2, ErbB2); 2 to EGFR; and one each against CD30, CD52, VEGF, epithelial cell adhesion molecule (EpCAM), cytotoxic T lymphocyte-associated protein 4 (CTLA4), and tumor necrosis factor ligand superfamily member 11 (TNFSF-11 or receptor activator of nuclear factor κ -B ligand [CD254] best known as RANKL).^{6,7}

Adverse Events

The small chemotherapeutic targeted drugs and targeted chimeric proteins (see [Table 7](#)) and mAbs (see [Table 8](#)) are considered separately.

Small chemotherapeutic drugs and cytotoxic chimeric proteins

Although it is true to say that targeted therapies generally produce less collateral damage to patients than nontargeted chemotherapies, for example, less nausea, vomiting, asthenia, diarrhea, and cytotoxic effects, the former still induce a wide range of adverse effects, only a few of which are true hypersensitivities.^{3,106} [Table 7](#) details the systemic and cutaneous reactions of a representative drug from each of the 6 different categories of signal transduction inhibitors; the proteasome inhibitors; 4 different categories of drugs affecting sex hormones; the targeted antifolate drugs; and targeted cytotoxic chimeric proteins. [Table 9](#), assembled from recorded adverse and hypersensitivity reactions of the large number of different non-mAb targeted agents currently being administered, summarizes the major hematologic, respiratory, cardiovascular, gastrointestinal, dermatologic, and other adverse events. Cytopenias occur less often and are less severe than the reactions induced by, for example, nontargeted alkylating and antimetabolite drugs but several reactions more or less unique to the targeted therapies are seen, including a lengthened QT interval, decreased left ventricular ejection fraction (LVEF), and a hand-foot skin reaction¹⁰⁷ (a distinct entity from hand-foot syndrome or acral erythema induced by nontargeted drugs, such as capecitabine, docetaxel, oxaliplatin, and methotrexate⁶). Cardiac toxicities are being increasingly recognized with targeted therapies.¹⁰⁸ Asymptomatic and symptomatic cardiac events were reported in 1.6% and 0.2%, respectively, of 3689 patients treated with the HER2 inhibitor lapatinib, and the multikinase angiogenesis inhibitors sunitinib and sorafenib have been associated with heart failure and hypertension, LVEF decrease, and a 6-fold higher chance of hypertension, respectively.¹⁰⁸ Mucocutaneous reactions to

Table 8
Hypersensitivity/adverse reactions of registered mAbs used for cancer therapy

Monoclonal Antibody ^a Generic ^b and Trade Names	Target ^c	Approved Indications	Hypersensitivity ^d /Adverse ^e Reactions	References ^f
Catumaxomab ^g (Removab)	EpCAM ^h /CD3 ⁱ	Malignant ascites	<i>Systemic</i> : cytopenias, CRS, SIRS, hepatotoxicity, abdominal disorders, pyrexia, infections, immunogenicity, dyspnea <i>Cutaneous</i> : rash, erythema, allergic dermatitis, hyperhidrosis, pruritus	⁹⁰
Ibritumomab tiuxetan ^j (Zevalin)	CD20 ^k	Non-Hodgkin lymphoma	<i>Systemic</i> : IR, severe cytopenia, infections, immunogenicity, secondary malignancies <i>Cutaneous</i> : exfoliative dermatitis, bullous dermatitis, EM, SJS, TEN	⁹¹
Tositumomab- ¹³¹ I ^l (Bexxar)	CD20	Non-Hodgkin lymphoma	<i>Systemic</i> : severe cytopenias, IR, hypothyroidism, infection, immunization, secondary malignancies, fetal harm, anaphylaxis <i>Cutaneous</i> : rash, pruritus, sweating, exfoliative dermatitis	⁹²
Rituximab (MabThera, Rituxan)	CD20	Non-Hodgkin lymphoma	<i>Systemic</i> : IR, TLS, renal toxicity, pulmonary events, ^m cardiac events, bowel obstruction and perforation, neutropenias, infections, PML, RA, SS, HBR, anaphylaxis <i>Cutaneous</i> : paraneoplastic pemphigus, lichenoid dermatitis, vesiculobullous dermatitis, SJS, TEN	^{7,93,94}
Ofatumumab (Arzerra)	CD20	Chronic lymphocytic leukemia	<i>Systemic</i> : cytopenias, IR, infections, pneumonia, intestinal obstruction, HBR, pyrexia, dyspnea, cough, diarrhea, fatigue, PML <i>Cutaneous</i> : rash, urticaria, hyperhidrosis	⁹⁵
Brentuximab vedotin ⁿ (Adcetris)	CD30 ^o	Anaplastic large cell lymphoma, Hodgkin lymphoma	<i>Systemic</i> : cytopenias, IR, TLS, immunogenicity, fetal harm, PML, anaphylaxis, PN <i>Cutaneous</i> : rash, pruritus, SJS, alopecia	⁹⁶
Cetuximab (Erbixux)	EGFR ^p	Colorectal, head and neck cancers	<i>Systemic</i> : IR, pulmonary events, ^m cardiopulmonary arrest, electrolyte imbalance, infection, GI, anaphylaxis	^{93,97}

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Table 8
(continued)

Monoclonal Antibody ^a Generic ^b and Trade Names	Target ^c	Approved Indications	Hypersensitivity ^d /Adverse ^e Reactions	References ^f
			<i>Cutaneous</i> : acneiform rash, nail changes, xeroderma, paronychia inflammation, pruritus	
Panitumumab ^g (Vectibix)	EGFR	Colorectal cancer	<i>Systemic</i> : IR, pulmonary events, ^r pulmonary embolism, electrolyte depletion, GI, fatigue <i>Cutaneous</i> ^s : rash, dermatitis acneiform, erythema, exfoliation, paronychia, skin fissures, photosensitivity, xerosis, pruritus	93,98
Bevacizumab (Avastin)	VEGF ^t	Colorectal, lung, kidney, brain cancers	<i>Systemic</i> : IR, pulmonary events, ^m GI perforation, hemorrhage, wound healing, non-GI fistula, arterial thromboembolic events, hypertension, necrotizing fasciitis, proteinuria, reversible posterior leukoencephalopathy <i>Cutaneous</i> : exfoliative dermatitis, alopecia	99
Pertuzumab (Perjeta)	HER2 ^u	Metastatic breast cancer	<i>Systemic</i> : IR, cytopenias, hypersensitivity/anaphylaxis, LVD, embryo-fetal toxicity, GI, PN <i>Cutaneous</i> : rash, paronychia, pruritus, alopecia	100
Trastuzumab (Herceptin)	HER2	Breast cancer	<i>Systemic</i> : IR, neutropenia, ^v anemia, pulmonary events, ^m embryo-fetal toxicity, cardiomyopathy, ^w LVD, GI, anaphylaxis/angioedema <i>Cutaneous</i> : rash, nail disorders, pruritus	93,101
Trastuzumab emtansine ^x (Kadcyla)	HER2	Advanced metastatic breast cancer	<i>Systemic</i> : hepatotoxicity, pulmonary events, thrombocytopenia, fetal harm, LVD, neurotoxicity, hypersensitivity/IR <i>Cutaneous</i> : rash, pruritus	102
Alemtuzumab ^y (Campath-1H)	CD52 ^z	Chronic lymphocytic leukemia	<i>Systemic</i> : IR, cytopenias, pulmonary events, ^m infections, ^{aa} immunogenicity, cardiac events <i>Cutaneous</i> : rash, urticaria, erythema, pruritus	103
Denosumab (Prolia, Xgeva)	RANKL ^{ab}	Bone metastases, giant cell tumor of the bone	<i>Systemic</i> : hypocalcemia, embryo-fetal toxicity, ONJ & osteomyelitis, dyspnea, fatigue/asthenia <i>Cutaneous</i> : rash, pruritus, dermatitis, eczema	104
Ipilimumab (Yervoy)	CTLA-4 ^{ac}	Metastatic melanoma	<i>Systemic</i> : IMR, diarrhea, fatigue <i>Cutaneous</i> : rash, pruritus, dermatitis	105

Abbreviations: CRS, cytokine release syndrome; CTLA-4, cytotoxic T lymphocyte-associated protein 4; EM, erythema multiforme; EpCAM, epithelial cell adhesion molecule; GI, gastrointestinal symptoms (eg nausea, diarrhea, vomiting, constipation, and so forth); HBR, hepatitis B reactivation; IMR, immune-mediated reactions caused by T-cell activation and proliferation (enterocolitis, hepatitis, dermatitis, neuropathies, endocrinopathies); IR, infusion reactions; LVD, left ventricular dysfunction; ONJ, osteonecrosis of the jaw; PML, progressive multifocal leukoencephalopathy; PN, peripheral neuropathy; RA, rheumatoid arthritis; RANKL, receptor activator of nuclear factor kappa-B ligand (CD254); SIRS, systemic inflammatory response syndrome; SS, serum sickness-like reactions, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis; TLS, tumor lysis syndrome.

^a Approved by the Food and Drug Administration and/or European Medicines Agency.

^b Nomenclature: mAbs of murine origin are given the suffix *omab*; chimeric antibodies in which the V region is spliced into human C region is given the *ximab* stem; humanized antibodies with murine hypervariable region spliced into human antibody have the *zumab* stem; and antibodies with complete human sequence are given the *umab* stem.

^c Specificity of mAb.

^d Reactions known or suspected of having an immunologic basis.

^e Other adverse reactions with no clearly established, or yet to be demonstrated, immune mechanism (nausea, cough, diarrhea, fatigue, sweating, and so forth).

^f For additional references for all mAbs listed here see.⁷

^g Registered by the European Medicines Agency, Health Canada, and Ministry of Health, Israel but not the Food and Drug Administration. Catumaxomab is a bispecific mouse-rat hybrid (given the suffix *axomab*) recognizing both the epithelial cell adhesion molecule and CD3.

^h EpCAM, epithelial cell adhesion molecule. Expressed on epithelial and epithelial-derived neoplasms.

ⁱ CD3 is part of the T cell receptor (TCR) complex on T lymphocytes.

^j With Yttrium-90 or Indium-111. Tiuxetan is a chelator.

^k Expressed on B lymphocytes where it aids optimum B cell response to T-independent antigens.

^l Kills B cells with ¹³¹I.

^m See Table 9.

ⁿ Conjugated to cytotoxic monomethyl auristatin E (MMAE).

^o CD30 is a cell membrane protein of the tumor necrosis receptor family. Expressed on activated T and B lymphocytes.

^p EGFR, epidermal growth factor receptor (HER1, ErbB-1).

^q Not indicated for use in combination with chemotherapy because of the increased toxicity.

^r See Table 9. It should be discontinued in patients developing interstitial lung disease, pneumonitis, and lung infiltrates.

^s The most common drug-induced reactions following this mAb are skin toxicities.

^t VEGF, vascular endothelial growth factor.

^u HER2, human epidermal growth factor receptor 2. Also known as Neu, ErbB2, CD340, or p185.

^v Highest risk with myelosuppressive therapy.

^w Greatest risk (left ventricular dysfunction) when administered with anthracyclines.

^x Called Ado-trastuzumab emtansine in the United States to distinguish from trastuzumab. Trastuzumab linked to the cytotoxin mertansine (deacetyl mercaptomaytansine [DM1]), a tubulin inhibitor.

^y Withdrawn from the United States and Europe in 2012 to be relaunched for multiple sclerosis (MS).

^z CD52 is present on the surface of mature lymphocytes and associated with some lymphomas.

^{aa} In particular *Pneumocystis jiroveci*, cytomegalovirus (CMV), Epstein-Barr virus (EBV), and herpes virus.

^{ab} RANKL, receptor activator of nuclear factor kappa-B ligand (CD254), a member of the tumor necrosis factor cytokine family.

^{ac} CTLA-4, cytotoxic T-lymphocyte antigen 4 (CD152). Binds CD80/CD86 on antigen-presenting cells.

Table 9 Summary of major adverse effects of targeted anticancer chemotherapies						
Targeted Therapy	Hematologic	Respiratory	Cardiovascular	GI	Dermatologic	Other
Multikinase Abl inhibitors ^a	Neutropenia; thrombocytopenia	Pneumonitis/pulm edema/alveolar damage; pulm hypertension	↓LVEF ^b /congest heart failure; QT prolongation	Mucositis/stomatitis; diarrhea/colitis	Rash ^c	Hypoglycemia; ↑transaminase; hyperlipasemia; hyperphosphatemia
EGFR inhibitors ^d	—	Pneumonitis/pulm edema/alveolar damage	—	Mucositis/stomatitis; diarrhea/colitis	Rash ^c ; HFSR ^e	Ocular - corneal abnormalities; conjunctivitis
Angiogenesis inhibitors ^f	Neutropenia; thrombocytopenia	Pneumonitis/pulm edema/alveolar damage	↓LVEF/congest heart failure; QT prolongation; hypertension; thromboembolic events	Mucositis/stomatitis; diarrhea/colitis	Rash; HFSR ^e	Hypothyroidism; hypoglycemia; ↑transaminase; hyperlipasemia; hypophosphatemia; hypomagnesemia
HER2 inhibitors ^g	—	Pneumonitis/pulm edema/alveolar damage	↓LVEF/congest heart failure	Mucositis/stomatitis; diarrhea/colitis	Rash	↑transaminase
mTOR inhibitors ^h	Neutropenia; thrombocytopenia	Pneumonitis/pulm edema/alveolar damage	—	Mucositis/stomatitis	Rash	↑transaminase; hyperglycemia; hypophosphatemia; hypercholesterolemia; hypertriglyceridemia

HDAC inhibitors ⁱ	Neutropenia; thrombocytopenia	—	QT prolongation	—	Rash	—
RXR agonists ^j	Neutropenia	—	—	—	Rash	↑ transaminase; hypothyroidism; hypercholesterolemia; hypertriglyceridemia; hypoglycemia
Proteasome inhibitors ^k	Thrombocytopenia	Pneumonitis/pulm edema/alveolar damage; pulm hypertension	—	—	Rash	Neuropathy; pyrexia; infections (herpes zoster); ↑ transaminase

For targeted drugs with hormonal effects and targeted antifolate drugs see.³

Abbreviations: Congest, congestive; GI, gastrointestinal; HDAC inhibitors, histone deacetylase inhibitors; HFSR, hand-foot skin reaction; LVEF, left ventricular ejection fraction; mTOR, mammalian target of rapamycin; pulm, pulmonary; RXR, retinoid X receptor.

^a For example, imatinib, nilotinib, dasatinib, and ponatinib.

^b LVEF, left ventricular ejection fraction.

^c Papulopustular rash, sometimes with pruritus, the most common dermatologic event.

^d For example, erlotinib, gefitinib, vandetanib, cetuximab, and panitumumab.

^e HFSR, hand-foot skin reaction, not to be confused with hand-foot syndrome or acral erythema.

^f Sunitinib, sorafenib, axitinib, ponatinib, and pazopanib; also includes ligand binders, (eg, aflibercept, bevacizumab).

^g For example, lapatinib, pertuzumab, and trastuzumab.

^h For example, everolimus and temsirolimus.

ⁱ Histone deacetylase inhibitors (eg, romidepsin, vorinostat).

^j Retinoid X receptor agonists (eg, bexarotene).

^k For example, bortezomib and carfilzomib.

Data from Baldo BA, Pham NH. Adverse reactions to targeted and non-targeted chemotherapeutic drugs with emphasis on hypersensitivity responses and the invasive metastatic switch. *Cancer Metastasis Rev* 2013;32:723–61; and Dy GK, Adjei AA. Understanding, recognizing, and managing toxicities of targeted anti-cancer therapies. *CA Cancer J Clin* 2013;63:249–79.

EGFR inhibitors, particularly a papulopustular rash, pruritus, xerosis, pigmentary changes, fissures on fingers and toes, alopecia, trichomegaly of the eye lashes, paronychia, stomatitis, and mucositis occur fairly commonly.¹⁰⁹

Although systemic and cutaneous responses to denileukin diftitox⁸⁶ are relatively few, with most reactions being infusion related (incidence ~70%) and vascular leak syndrome (27%), aflibercept has been implicated in causing hypertension and thromboembolic events. Other side effects with the drug, namely, mucositis/stomatitis, diarrhea, neutropenia, thrombocytopenia, and elevated transaminase levels, occur more often in combination therapy (eg, with 5-fluoruracil or FOLFIRI [FOL, folinic acid; F, fluoruracil; IRI, irinotecan]) than with chemotherapy alone.^{87,106} One fatal case of toxic epidermal necrolysis (TEN) occurred following the administration of denileukin diftitox.¹¹⁰

Hypersensitivity is a loosely used term sometimes incorrectly employed to describe responses that have no immune basis or component, whereas other reactions where the term would be appropriate have been overlooked.³ There are far fewer reports of each of the 4 types of hypersensitivities classified according to Coombs and Gell¹¹¹ for targeted than for nontargeted chemotherapeutic drugs, but this may be, in part, a reflection of the so-far inadequate study of many targeted drug-induced responses and because of their more recent introduction. Specific examples of reactions shown in **Box 4** summarize the current general view of the 4 different hypersensitivity responses seen to the small, targeted drugs.

mAbs

mAbs are also better tolerated than conventional antineoplastic drugs; but again, reactions to the agents are quite diverse, ranging from mild gastrointestinal symptoms and transient rash to anaphylaxis, severe cardiac and pulmonary toxicities, cytopenias, and life-threatening toxidermias (see **Table 8**).^{6,7,93,106} Several reactions to mAbs are immune mediated (see later discussion); some may or may not have an immune component (eg, some infusion reactions/cytokine release syndrome [CRS] and systemic inflammatory response syndrome [SIRS]), whereas heart and some pulmonary, kidney, hepatic, and neurologic toxicities seem to be caused by nonimmune mechanisms (**Box 5**).^{7,41,93}

Even with the development of humanized and fully human mAbs, the possibility of generating anti-idiotypic antibodies remains⁷; although type I anaphylactic reactions

Box 4

Hypersensitivity reactions to targeted chemotherapeutic drugs (for additional references see³)

- Type I IgE antibody-mediated reactions seen more often with tamoxifen, aromatase inhibitors exemestane and letrozole, gonadotropin-releasing hormone agonists goserelin and leuprolide, the mTOR inhibitor everolimus, and tyrosine kinase inhibitor bosutinib
- Type II hypersensitivities represented in few reports of autoimmune hypothyroidism and immune thrombocytopenia to tyrosine kinase inhibitors, especially sunitinib^{112,113}
- Type III hypersensitivities also infrequently described: chiefly drug-induced vasculitis to tamoxifen and aromatase inhibitors (eg, anastrozole) and erlotinib (implicated in at least 14 cases)
- Type IV hypersensitivities reported to imatinib (drug reaction with eosinophilia and systemic symptoms [DRESS]); imatinib and exemestane (acute generalized exanthematous pustulosis); imatinib, exemestane, and letrozole (erythema multiforme); tamoxifen (erythema multiforme and Stevens-Johnson syndrome [SJS]); imatinib and vandetanib (SJS); imatinib letrozole, palatexate, and bortezomib (TEN); erlotinib, sorafenib, and bexarotene (bullous eruptions)

Box 5**Nonimmune-mediated adverse events to mAbs used for cancer therapy**

- Mechanisms of mAb-induced thrombocytopenia, neutropenia, hemolytic anemia, and vasculitis are often not investigated. Some may be immune mediated (see [Box 6](#)).
- MAb-induced lung diseases, drug-induced lung disease (DILD): The mechanisms are generally not known; therefore, classification on the basis of pathogenesis is difficult (see [Box 7](#)).
- Cardiac events occur with at least 5 mAbs: trastuzumab (↓LVEF, cardiomyopathy); pertuzumab (↓LVEF); bevacizumab (↓LVEF, hypertension, thromboembolic events, ↑ heart failure)^{106,108}; rituximab (cardiac arrhythmias); cetuximab (cardiopulmonary arrest in patients exposed to radiation therapy).
- Tumor lysis syndrome is well known after brentuximab vedotin and rituximab.
- Progressive multifocal leukoencephalopathy is occasionally seen after brentuximab, ofatumumab, and especially rituximab.
- Papulopustular (acneiform) eruptions occur to EGFR-targeted mAbs (eg, cetuximab and panitumumab).

Data from Baldo BA. Adverse events to monoclonal antibodies used for cancer therapy. Focus on hypersensitivity responses. Oncoimmunology 2013;2(10):e26333. <http://dx.doi.org/10.4161/onci.26333>; and Hansel TT, Kropshofer H, Singer T, et al. The safety and side effects of monoclonal antibodies. Nat Rev Drug Discov 2010;9:325–38.

might be expected, these responses to therapeutic mAbs are relatively uncommon. Other adverse reactions to mAbs, such as urticaria, serum sickness, SJS, TEN, and autoimmune diseases (eg, ipilimumab-induced autoimmune enterocolitis),¹¹⁴ are clear examples of an immune-mediated reaction. However, some cytopenias, pulmonary and liver toxicities, infections, some other systemic responses, and cutaneous reactions are often difficult to categorize and may (eg, infusion reactions/CRS and SIRS) or may not (eg, tumor lysis syndrome [TLS], some cytopenias and pulmonary reactions, heart, embryo-fetal and neurologic toxicities) have an immune component.^{3,7} [Box 6](#) summarizes known hypersensitivities to the mAbs currently administered as cancer therapies; but it is clear that mechanisms of many reactions induced by

Box 6**Hypersensitivity reactions to mAbs used for cancer therapy**

- Type I: There is a low incidence of reactions. Chimeric molecules, catumaxomab, ibritumomab, tositumomab, cetuximab, rituximab, and brentuximab carry warnings. Anaphylaxis is reported for cetuximab, rituximab, brentuximab, ibritumomab, trastuzumab, pertuzumab, and tositumomab.
- Type II: There is little or no good evidence for immune thrombocytopenia. Rituximab-induced late-onset neutropenia may be immune mediated. Autoimmune hemolytic anemia is induced by rituximab and alemtuzumab.
- Type III: Cellular and humoral processes may be involved in some cases of mAb-induced vasculitis. Chimeric mAbs can induce serum sickness (eg, rituximab).
- Type IV: Rare reactions seem to be confined to ibritumomab, brentuximab, and especially rituximab (SJS, TEN, lichenoid dermatitis, vesiculobullous dermatitis, and paraneoplastic pemphigus). Dermatitis is induced by catumaxomab, bevacizumab, denosumab, ipilimumab, panitumumab, and tositumomab; they may be type IV reactions, but the mechanisms are not established.

Data from Refs. ^{6,7,93,106}

individual mAbs remain inadequately investigated, and the list of mAb-induced hypersensitivities is likely to be extended. **Box 7** lists the mAbs implicated in pulmonary adverse events. Rituximab is the agent most commonly involved causing, in particular, bronchiolitis obliterans organizing pneumonia (BOOP), followed by interstitial pneumonitis, acute respiratory distress syndrome (ARDS), and hypersensitivity pneumonitis.

Diagnosis

Diagnostic procedures for hypersensitivities to targeted chemotherapeutic agents are generally not well developed, widely applied, or validated. For type I and IV reactions, few (if any) convincing skin test studies with sufficient numbers of patients seem to have been carried out.^{3,6,7} Some immunoassays to aid the diagnosis of immune thrombocytopenia by detecting platelet-reactive serum IgE antibodies are available in only a few laboratories but, in general, the tests are not standardized, do not detect the drug-dependent antibodies, often present technical difficulties, and can produce false-positive results. The time delay in obtaining results in an urgent situation is also a major drawback. Some recommendations for testing for immune thrombocytopenia have been published.¹¹⁵ Although neutrophil antigens involved in immune neutropenia have been identified, immunoassays to aid the diagnosis of immune-mediated neutropenia and agranulocytosis are not widely available. The monoclonal antibody immobilization of granulocyte antigens assay (MAIGA) seems to be the most specific test; but again, technical difficulties, autoantibodies, and drug-dependent antibodies can be a problem.¹¹⁶ Diagnosis of drug-induced vasculitis, liver injury, lung disease, and some delayed cutaneous reactions all present difficulties because of a lack of specific tests, suitable laboratory markers, and/or convincing experimental models (see review³ for discussion and references).

Premedication and Desensitization

Corticosteroids, often dexamethasone, and antihistamines, such as diphenhydramine and cimetidine/ranitidine/famotidine, are generally given in premedication protocols

Box 7

Pulmonary adverse events caused by mAbs

- *-ximabs*
 - Cetuximab: interstitial pneumonitis
 - Rituximab: ARDS, BOOP, bronchospasm, diffuse alveolar hemorrhage, hypersensitivity pneumonitis
- *-zumabs*
 - Alemtuzumab: bronchospasm, diffuse alveolar hemorrhage, pulmonary infections
 - Bevacizumab: anaphylaxis/bronchospasm, pulmonary hemorrhage from tumor site
 - Trastuzumab: ARDS, BOOP, dyspnea, interstitial pneumonitis, pleural effusions, pulmonary infiltrates/pulmonary fibrosis/pulmonary edema
- *-umabs*
 - Panitumumab: interstitial lung disease, lung infiltrates, pneumonitis, pulmonary fibrosis

Data from Baldo BA. Adverse events to monoclonal antibodies used for cancer therapy. Focus on hypersensitivity responses. Oncoimmunology 2013;2(10):e26333. <http://dx.doi.org/10.4161/onci.26333>.

often 12 and 6 hours before infusions of drugs. The corticosteroid is sometimes given for several days before infusion.⁶

As already emphasized,¹¹⁷ desensitization has become a cornerstone in the management of hypersensitivity reactions to chemotherapeutic drugs and mAbs. By comparison with the nontargeted drugs, there are, as yet, fewer published studies on desensitization for the targeted chemotherapeutic drugs. Desensitization to the multi-kinase inhibitor sunitinib was accomplished following premedication with prednisone and promethazine and 10 escalating dosage steps beginning with a dose of 0.05 mg.¹¹⁸ Most procedures have been undertaken with imatinib. Starting with a dose of 0.005 mg and building to a total of 400 mg, desensitizations were achieved with gradual dose escalations over 10 weeks in one case and over 5 days in another.¹¹⁹ Success has also been reported using a 4-hour outpatient oral protocol beginning with 10 ng of imatinib and proceeding with increasing doses every 10 minutes.¹²⁰

More data are available for mAbs. Successful desensitization to cetuximab commenced with premedication with prednisolone 12 hours and 1 hour before and diphenhydramine 30 minutes before commencement. From a starting dose of 0.001 mg cetuximab, doses were doubled every 15 minutes before a final dose of 325 mg at step 20, giving a cumulative dose of 844 mg. Any reactions were managed with diphenhydramine, a 30-minute waiting period, and dose and infusion reductions.¹²¹ In another protocol, a 5-step procedure was used beginning with 5.07 mg and ending with 694.0 mg for a total of 769.9 mg.¹²² In a rapid desensitization protocol for rituximab, patients first received premedication with H1 and H2 antihistamines and sometimes acetaminophen and/or corticosteroids before undergoing a 12-step procedure in which the dose was increased every 15 minutes from an initial dose of 0.022 mg. At step 12, the dose of 1020.5 mg represented approximately half of the total desensitization time taken and 92% of the total dose given. Most reactions that occurred were seen at this stage and responded to antihistamine treatment and an infusion pause.²⁷ Note that a negative skin test did not override a strong clinical history of a hypersensitivity reaction in determining whether or not to desensitize.¹²² Unlike other hypersensitivity reactions to mAbs, particularly rituximab, reactions to trastuzumab are usually seen after multiple exposures.¹²³ Here again, a 12-step protocol has been used, with 92.3% being administered at the final step.^{27,123} In a recently published rapid desensitization procedure for antineoplastic agents, including rituximab,³² starting doses were 80% higher than the previously used successful 12-step procedures. It should be remembered, however, that higher starting doses are generally accompanied by higher potential risks.

FUTURE CONSIDERATIONS

The realization that antiangiogenic therapy, initially effective by inhibiting vascularization and tumor growth, may lead on to the reverse effect of enhanced tumor growth, invasiveness, and distal metastasis highlights the need to understand how tumor resistance develops.¹²⁴ This resistance of tumors has consequences for the appearance of some changed patterns of drug-induced adverse effects as new drugs are sought to inhibit hypoxia signaling. Combination therapies (using, for example, cytotoxic topoisomerase, mTOR, histone deacetylase (HDAC), and proteasome inhibitors) are being increasingly used to overcome the resistance.³ Other possible new therapies that will each bring their own spectrum of adverse reactions include the introduction of further soluble decoy receptors for growth factors; drugs that inhibit VEGF, angiopoietins, placental growth factor, hypoxia-inducible factor-1 α (HIF-1 α), c-Met, E-cadherin, and matrix degrading enzymes; targeting of angiopoietin-Tie2

signaling; and the study of inhibitors of vascular integrin for antiangiogenic therapy.³ Lastly, the terminology used to define hypersensitivity needs to be standardized so that investigators in oncology, immunology, and allergy can work from a common definition to distinguish true hypersensitivities from other adverse reactions. Misuse of the term *hypersensitivity* is particularly apparent in cancer chemotherapy; the fact that allergists and clinical immunologists are often so little involved in the diagnosis and management of adverse reactions is to the detriment of patients, the disciplines of oncology and allergology, the interpretation of observed reactions, and perhaps even the integrity of some of the data from clinical trials.³

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