

Hypersensitivity Reactions to Chemotherapeutic Drugs

Gillian M. Shepherd

*Weill Medical College of Cornell University, New York, NY
E-Mail: gshepherdmd@aol.com*

Abstract

There is an ever-increasing number of therapeutics used to treat cancer. A recent publication listed 86 currently available antineoplastic medications. Despite this large number, hypersensitivity reactions are not common except with platinum compounds (cisplatin, carboplatin), epipodophyllotoxins (teniposide, etoposide), asparaginase, taxanes (paclitaxel), and procarbazine. Doxorubicin and 6-mercaptopurine are occasionally associated with hypersensitivity reaction. Comparable reactions with other chemotherapeutic agents are uncommon; many are only anecdotal reports. Reactions associated with individual drugs are discussed in detail.

The mechanisms responsible for most of these reactions are not known, as they have generally not been evaluated. The term "hypersensitivity" is widely used in the chemotherapy literature without a common definition. Hypersensitivity is defined here as an unexpected reaction with signs and symptoms not consistent with known toxicity of the drug. Most reactions are coincident with or within hours of drug administration. Almost all are associated with parenteral administration. Symptoms include flushing, alterations in heart rate and blood pressure, dyspnea and bronchospasm, back pain, fever, pruritus, nausea and all types of rashes. Some cases may be due to non-immune mediated release of histamine or cytokines, as many patients can subsequently tolerate re-exposure after pretreatment with steroids and antihistamine, and slow readministration of the drug. This is more compatible with a graded challenge, than desensitization and is generally successful for taxanes, less so for platinum compounds.

In most cases hypersensitivity reactions are associated with the specific chemotherapeutic drug. Reaction rates may vary with different forms of the drugs, e.g. pegylated. Occasionally excipients such as Cremaphor EL may induce hypersensitivity reactions.

Index Entries:

Hypersensitivity; allergy; chemotherapy; desensitization; drug asparaginase; platinum compounds; epipodophyllotoxins; taxanes.

Table 1
Usual Drugs of Choice for Common Cancers

Lung	Paclitaxel
	Cisplatin/carboplatin
Gastrointestinal	Flurouracil
Breast	Cyclophosphamide
	Methotrexate
	Flurouracil
	Doxorubicin
Gynecological	Paclitaxel
	Cisplatin/carboplatin
	Paclitaxel
Hematologic	Vincristine/vinblastine
	Asparaginase
	Doxorubicin/daunorubicin
	Cyclophosphamide
	Cytarabine/fludarabine
	Etoposide
	Chlorambucil/melphalan
	Methotrexate
	Bleomycin

Introduction

There is an ever-increasing number of therapeutics used to treat cancer. A recent publication listed 86 currently available anti-neoplastic medications (1). Despite this large number, hypersensitivity reactions are not common except with platinum compounds (cisplatin, carboplatin), epipodophyllotoxins (teniposide, etoposide), asparaginase, taxanes (paclitaxel, docetaxel), and procarbazine (2). Doxorubicin and 6–mercaptapurine are occasionally associated with hypersensitivity reactions. Comparable reactions with other chemotherapeutic agents are rare, and many are only anecdotal reports. In one small series of 32 patients with gynecological malignancies, carboplatin induced hypersensitivity reactions in 16 patients, followed by paclitaxel (10), cisplatin (4), and bleomycin (1) (3). Table 1 lists the usual drugs of choice for common malignancies.

The mechanisms responsible for most of these reactions are unknown, as they have generally not been evaluated. The term “hypersensitivity” is widely used in the chemotherapy literature without a common definition. Hyper-

sensitivity is defined here as an unexpected reaction with signs and symptoms that are not consistent with known toxicity of the drug. Most reactions are coincident with or within hours of drug administration. Almost all are associated with parenteral administration. Symptoms include flushing, alterations in heart rate and blood pressure, dyspnea/bronchospasm, back pain, fever, pruritus, nausea, and all types of rashes (3). Clearly it is difficult to evaluate these reactions through prospective studies. Some reactions may be caused by non-immune-mediated release of histamine or cytokines, as many patients can subsequently tolerate reexposure after pretreatment with steroids and antihistamine, plus slow readministration of the drug. This is more compatible with a graded challenge than desensitization. It is generally successful for taxanes, but less so for platinum compounds (2).

Reactions associated with specific drugs are listed in the following sections; those responsible for more frequent reactions are listed first. Multiple factors affect reaction rates, including route, rate of administration, previous exposure, form of the drug (e.g., pegylated [structurally combined with polyethylene glycol] or not, presence of excipients such as Cremaphor EL), whether the drug is given as a single agent or in combination, coincident medications that may affect metabolism of the chemotherapeutic drug, concurrent auto-immune disease, and possibly the nature of the underlying malignancy. For these reasons, it is difficult to chart comparative hypersensitivity reaction rates for these drugs. A listing of common drugs associated with hypersensitivity reactions is provided in the following section.

Chemotherapeutic Drugs Frequently Associated with Hypersensitivity Reactions

Asparaginase

L-asparaginase is an enzyme primarily used to treat acute lymphoblastic leukemia (ALL), and

is associated with a high frequency of hypersensitivity reactions. If a patient has a reaction, changing the route of administration, form, or source of the drug, or undergoing desensitization to L-asparaginase, usually results in most patients completing the prescribed course. The reaction rate with intravenous (iv) administration is very high. For this reason, L-asparaginase is almost always given now by the intramuscular (im) or subcutaneous (sc) route, which is associated with a lower reaction rate. Most reactions occur within one to several hours after administration and include signs and symptoms typical of anaphylaxis, sometimes fatal. Intravenous administration is associated with a hypersensitivity reaction rate of 6–43% (4). “Hypersensitivity” in these studies ranges from anaphylaxis to 2 cm erythema at the site of an injection, persisting for 10 min. Reactions are more frequent if the patient has received the drug daily or 3× per week for 2 wk (4). In all cases, reactions are more common if the drug is given alone and in high doses (5). In a 1998 series, 197 adult patients with ALL were given sc doses of L-asparaginase twice weekly for 7 wk. Twenty-one developed severe reactions and stopped the drug, and 7 had milder reactions and were able to complete the course for a total adverse reaction rate of 14% (27/197). The mean time to reaction was 7 d (range 1–11) (6). Retreatment is associated with an increased risk of reactions. In a 2001 article, 24% of 76 children with ALL developed clinical hypersensitivity reactions during reinduction treatment (7).

Because the hypersensitivity reaction rate is so high, especially with iv administration, skin testing with L-asparaginase is recommended before the first dose and any time thereafter that an interval of 1 wk or greater has elapsed between doses. The recommendation is 0.1 mL ID of a 20 IU/mL dilution of drug. A positive test is defined as a wheal or erythema appearing in the subsequent hour. This testing is not standardized, and reactions have occur-

red in skin test-negative patients. If the test is positive by these criteria, then it is recommended that the patient undergoes desensitization. A sample protocol is outlined in the *Physician's Desk Reference* (8).

Another approach to the patient who is sensitive to L-asparaginase is to switch to the polyethylene glycolated (PEG) form, pegaspargase, which is better tolerated, especially when given intramuscularly. It is specifically indicated for treatment in patients who are sensitive to the native drug. If given intramuscularly, approx 70% of these patients will tolerate the PEG form, vs 90% of patients with no history of reactions to the native drug; if given intravenously, approx 40% of sensitive patients tolerate it vs 90% of non-sensitive patients. There is a theoretical concern about giving a long-acting drug, if there is a chance of an immune-mediated reaction to the drug.

L-asparaginase is derived from *Escherichia coli* (*E. coli*). It is also made from *Erwinia*, a parasitic bacteria. These two preparations are immunologically distinct (4). In the series previously discussed (6), of the 21 patients who had severe reactions, 20 were switched to *Erwinia* L-asparaginase, and 18/20 were able to complete the course. Granulocyte-colony-stimulating factor (G-CSF), used to treat myelosuppression, is also derived from *E. coli*. Stone et al. (4) documented two patients in 1998 who were the first two documented cases of anaphylaxis to pegaspargase, who had positive reactions to G-CSF (ID skin test in one and systemic urticaria in the other 6 h after a negative skin test). Both patients did not react on skin testing to a structurally distinct molecule, granulocytemacrophage colony-stimulating factor (GM-CSF), which is made from a mold, not from *E. coli*. This finding suggests that these patients may have reacted to a bacteria-specific polypeptide. If patients have a history of reaction to L-asparaginase and require treatment for myelosuppression, this report suggests that GM-CSF should be used preferentially.

The mechanism responsible for the immediate reactions is unclear. IgE antibody has been demonstrated in some patients, and complement activation has also been noted (5). Particulate material can occasionally develop in the reconstituted drug if left standing, which could conceivably contribute or cause reactions—although this has not been reported. IgG anti-asparaginase has been documented and may be correlated with sensitivity. In a study of 152 children on d 29 of *E. coli* L-asparaginase for ALL, 35% had IgG antibody specific for asparaginase. Half of this group had a hypersensitivity reaction to the drug vs 18% of patients with no antibody. Of the group that reacted, 80% of those later given the *Erwinia* L-asparaginase tolerated it (9).

If there is a specific antigen, it is unclear whether it is unique to L-asparaginase, as different routes of administration are associated with different reaction rates. Additionally, patients who have had reactions to L-asparaginase can often tolerate the long-acting PEG-asparaginase (5). It is also possible that reactions are related to bacteria-specific polypeptides, as two reported patients sensitive to asparaginase reacted by skin testing to another *E. coli* product, and most *E. coli*-sensitive patients can tolerate L-asparaginase produced in *Erwinia*.

Summary

At present, first-line treatment is usually im *E. coli* L-asparaginase. Skin testing should be done before the drug is given. This testing is not standardized, and reactions have occurred in skin test-negative patients, so the drug must be administered in a facility that is capable of treating anaphylaxis. Small test doses are not predictive of later reactions. There is no data on the utility of pretreatment with steroids and antihistamines. If the patient has a serious reaction, they should be desensitized, change to the PEG form of the drug, or change from the common *E. coli* form to the *Erwinia* product.

Platinum Compounds (Cisplatin and Carboplatin)

These drugs are alkylating agents commonly used for treatment of gynecological tumors—particularly ovarian—and adenocarcinoma of the lung. Cisplatin was developed first, but carboplatin is now used more often. A high frequency of anaphylactic-like reactions has been reported, all occurring within minutes of administration in patients with prior exposure, generally after six courses. Symptoms include facial edema, bronchospasm, hypotension, and tachycardia. All have reversed with treatment, including epinephrine.

Zanotti et al. (10) have reported a 27% incidence of hypersensitivity reactions in patients who receive more than seven courses of carboplatin. In another 2001 review (11), of 194 adults treated for ovarian cancer for the first time with carboplatin, 16% developed symptoms that were compatible with a hypersensitivity reaction. These ranged from mild pruritus and erythema to immediate, generalized life-threatening anaphylaxis. Reactions occurred from the fourth to the eighth course. In contrast, 46 patients who received intraperitoneal (ip) carboplatin had no hypersensitivity reactions (the first case of a reaction after repeated ip administrations was reported in 1999 (12)). Those with non-life-threatening reactions were able to continue treatment. The 12 patients with severe reactions were unable to tolerate readministration of carboplatin, although four later tolerated cisplatin. A 1999 survey found very similar results; 12% (24/205) of patients had a hypersensitivity reaction with a wide range of symptoms; only one of three tolerated rechallenge (13).

A recent trial suggested skin testing may be predictive of the chance of developing a reaction (10). All patients receiving course #7 of carboplatin underwent skin testing 1 h prior to drug infusion. Testing was an intradermal injection of 0.02 mL of the full-strength drug. A positive reaction was defined as a hive of 5

mm with erythema. Their historical control group had a reaction rate of 27% after seven courses. They found 28% (13/47) of patients had positive skin tests. Ninety-six percent of the skin test-negative patients tolerated further courses of the drug.

If a patient has had a hypersensitivity reaction to a platinum drug, they will often have a repeat reaction with rechallenge. Pretreatment with steroids and antihistamines has not prevented these reactions (14). If they had a reaction to carboplatin, they may tolerate cisplatin, or vice versa, particularly if there is a negative skin test to the other. Another option is to desensitize the patient. This has been reported to be successful in three patients, but in one case it took 3 d (14). At the end, the positive skin test reverted to negative, supporting a true desensitization, rather than a graded challenge.

Summary

Both cisplatin and carboplatin are associated with anaphylactic-like symptoms in 10–27% of patients, generally occurring after 4–6 courses. Skin testing may predict reactions. Sometimes a patient who is sensitive to one will tolerate the other. Most patients react again if rechallenged. Desensitization has been successful in a small number of patients.

Epipodophyllotoxins (Teniposide = VM26, Etoposide = VP16)

Teniposide is used to treat neurological and hematologic malignancies. Etoposide is indicated for refractory testicular tumors and small-cell lung cancer. Teniposide differs from etoposide by the substitution of a thenylidene group on the glucopyranoside ring; there is no data to suggest cross-sensitization.

Both of these drugs induce hypotension in 1–2% of patients following rapid iv infusion, very similar to the situation with vancomycin. To prevent this, it is recommended the drugs be infused slowly over a period of 30–60 min with medical observation for 60 min. In addition

to hypotension, patients who experience immediate reactions can also experience fever, chills, urticaria, and bronchospasm. There appears to be an association between reactions and higher doses. Reactions generally occur with or shortly after infusion, and symptoms are typical of histamine release, although no specific IgE has been documented. Up to 33% of reactions have occurred with the first exposure (5). Symptoms generally respond to epinephrine, antihistamines, and steroids.

Teniposide is associated with a higher frequency of hypersensitivity reactions. A 1992 review noted an incidence ranging from 5 to 41%, although in the latter case, the reactions were very mild (5). In a 1991 study of 108 children with ALL, the risk of a hypersensitivity reaction was 52% for teniposide and 34% for etoposide (15). In a 1993 study of 45 adults with Hodgkin's, 51% developed a hypersensitivity reaction to etoposide coincident with the first or second dose with a median time of onset of 5 min (range 3–120). Signs and symptoms included flushing, hypotension, bronchospasm, and abdominal pain. Seventy-eight percent of the patients were rechallenged successfully with a slow rate of infusion and pretreatment with steroids and antihistamines (16).

Each mL of teniposide solution contains 10 mg of drug and 500 mg of Cremaphor EL, a polyoxyethylated castor oil added to solubilize the drug. This excipient is also added to paclitaxel (527/mL) and cyclosporin iv solution (650 mg/mL). In the latter case, allergic reactions are rare and mild, occurring less than 2% per course. There is currently no data specifically implicating Cremaphor EL as the culprit. More recently, Szebeni et al. (17) have shown that injection of this emulsifier at usual pharmacologic doses will induce micelles and needle-like structures formed mainly from the Cremophor EL. These micelles induce complement activation, which can be blocked by intravenous immunoglobulin (IVIG). However, in a teniposide study, basophil histamine release

occurred in children with the active drug and not the Cremophor EL (18). This has also been noted in a patient desensitized to paclitaxel, as noted here. Etoposide is generally associated with a lower frequency of reactions and has no Cremaphor EL, although its excipient, polysorbate 80, is suspected to induce some reactions (19).

Summary

Rapid infusion induces hypotension, which can be avoided by a slower rate. If a patient has a history of a reaction to one of these drugs, they can generally be successfully rechallenged via a slow, graded challenge with a prophylactic regimen of steroids and antihistamines (15). The drugs do not crossreact, but have different indications, so one cannot necessarily be substituted for the other.

Taxanes (Paclitaxel and Docetaxel)

Paclitaxel is used primarily for non-small-cell lung, breast, and gynecological malignancies. Docetaxel is a newer semisynthetic taxane. Severe anaphylactic reactions may occur in 2–4% of patients treated with paclitaxel and 2% of patients treated with docetaxel; thus, all patients require pretreatment with steroids and antihistamines *before each dose* of either drug. Symptoms are hypotension, dyspnea, systemic urticaria, and angioedema. Reactions typically occur with the first or second dose, and are occasionally fatal. They occur more frequently in patients with a history of atopy (20), although there is no evidence of specific IgE in this reaction. Pretreatment decreases the incidence of paclitaxel hypersensitivity reactions (21), although another report notes that 41% of patients who reacted did so despite pretreatment (22). A common pretreatment protocol is 40 mg of dexamethasone or equivalent orally 12 and 6 h before paclitaxel administration plus diphenhydramine and a histamine-2-receptor antagonist 30 min before the infusion (23). With this pretreatment, the reaction rate is usually 1–2% compared to 2–5% without pretreat-

ment (24). Recently, however, 132 patients were treated with only 10–20 mg of dexamethasone immediately prior to infusion, with no increase in the reaction rate (25).

If a patient has had a past reaction to paclitaxel and needs it again, there are two options. The first is desensitization. There are three reports in the literature totaling 15 patients. All were successfully given incremental doses with pretreatment, including steroids and antihistamines (22,26,27). The second possibility is to try docetaxel as an alternate (24). Bernstein (28) reviewed the literature to 2000, and determined that docetaxel is tolerated by most patients who have reactions to paclitaxel; however, it is also associated with a 2% incidence of anaphylactic reactions, and patients require pretreatment with steroids and antihistamines before administration. It has been suggested that this may be because of the drug vehicle, polysorbate-80 (29), similar to etoposide, as discussed above.

It is unclear whether paclitaxel reactions result from sensitivity to the drug or to the excipient, Cremophor EL, added to solubilize the drug. This excipient is also added to cyclosporin and tenoposide. One of the patients who was successfully desensitized to paclitaxel also showed evidence of basophil release with the drug, but not the Cremophor EL vehicle (22).

Summary

Two to four percent of patients experience anaphylactic-like reactions to paclitaxel that are most likely non-IgE-mediated. Histamine release occurs from basophils. Whether this results from a non-immune effect of the drug—similar to contrast media reactions—or is related to the formation of micelles from the Cremophor EL excipient in paclitaxel or a reaction to polysorbate-80 in docetaxel, is unknown. It is also possible that more than one mechanism may account for these reactions in different patients. If a patient has had a reaction to paclitaxel, desensitization or switching to docetaxel may be successful.

Procarbazine

Procarbazine is often used to treat brain tumors. It is only available in capsule form, which also contains mannitol, gelatin, and FD&C yellow dyes #6 and 10. In older series, 6–18% of treated patients developed macular-papular rashes or urticaria. None were able to continue treatment (5). In a report on 8 patients who had hypersensitivity reactions, 7 developed macular-papular rashes, 4 developed fever, and 3 had reversible liver function abnormalities. Two patients with past rashes were rechallenged, and developed life-threatening pulmonary infiltrates (30). There is one report of a fixed drug eruption (31). In a recent series of 83 patients on procarbazine for primary brain tumors, 20 experienced hypersensitivity reactions; all of these patients were coincidentally on cytochrome (CYP-3A)-enzyme enhancing anticonvulsants, especially phenobarbital. This enhances the metabolism of procarbazine to a reactive intermediate (32). The authors recommend use of newer anticonvulsants that do not induce CYP-3A as treatment if the patient is on procarbazine.

Patients can also experience lung toxicity, similar to allergic alveolitis with interstitial pneumonitis, infiltrates, and/or cough, sometimes with prominent eosinophilia. None of these sensitivities can be predicted thus far, and rechallenge in patients with these reactions has generally been unsuccessful (5), and may result in life-threatening symptoms (30).

Chemotherapeutic Drugs Occasionally Associated with Hypersensitivity Reactions

Anthracyclines (Doxorubicin, Daunorubicin, Idarubicin, and Epirubicin)

These agents—especially doxorubicin—are used to treat variety of cancers, including breast and hematologic. Hypersensitivity reactions characteristic of IgE-mediation are rarely

reported. Recently pegylated liposomal doxorubicin and daunorubicin have become available; they offer the advantage of longer circulation time, less cardiotoxicity, alopecia, nausea, and vomiting, but acute hypersensitivity infusion reactions have been reported in up to 9% of patients (33). During clinical trials with PEG daunorubicin, 14% of patients experienced back pain, flushing, and chest tightness within 5 min of the start of the infusion. They tolerated readministration at a slower rate. PEG doxorubicin is currently used for AIDS-related Kaposi's sarcoma and recurrent ovarian cancers (34). One patient experienced a life-threatening reaction within minutes of the first dose (35). The mechanism is unknown.

Mercaptopurine and Azathioprine

Mercaptopurine is used for maintenance treatment of leukemias and also for treatment of inflammatory bowel disease. Hypersensitivity reactions are rare in leukemia patients, but in a recent retrospective review, 16/591 (2.7%) of patients with inflammatory bowel disease had reactions during treatment (36). The most common symptom was fever (14/16 patients), which generally recurred with rechallenge. Six patients were placed on azathioprine as an alternative, and developed the same symptoms. Four were successfully “desensitized” via slow, graded readministration.

Azathioprine is an imidazolyl derivative of 6-mercaptopurine used primarily as an immunosuppressant. Allergic reactions are very rare.

Chemotherapeutic Drugs Rarely Associated with Hypersensitivity Reactions

Bleomycin

This drug is indicated for malignant pleural effusions and is also used for lymphomas, and squamous cell and testicular carcinomas. Approximately 1% of lymphoma patients develop hypotension, mental confusion, fever, chills, and wheezing after the first or second

dose. It may happen immediately or after several hours. The mechanism is unknown, and the symptoms generally respond to symptomatic treatment.

Chlorambucil and Melphalan

These drugs are alkylating agents derived from nitrogen mustard, and are used to treat leukemias—chlorambucil more often than melphalan. Chlorambucil is only available postoperatively; the inactive ingredients include corn and wheat starch. Reports of hypersensitivity reactions are rare. Most have involved delayed rashes, including toxic epidermal necrolysis (TEN), with associated systemic symptoms. In one case of a delayed reaction of exfoliative erythroderma and myalgias, the patient had a positive patch and lymphocyte transformation test (LTT), implying a delayed hypersensitivity mechanism (37). In all cases, patients subsequently tolerated another alkylating agent.

Melphalan is available intravenously and per os (PO). In a clinical study of 225 patients, 3.9% experienced anaphylactic-like symptoms after iv infusion (37a). Symptoms included urticaria and angioedema, with some cases of bronchospasm and hypotension. Other adverse reactions have been primarily dermal. Rare hypersensitivity reactions have also been noted with the oral form of melphalan.

Cyclophosphamide and Ifosfamide

Cyclophosphamide is an alkylating agent used widely for the treatment of breast, hematologic, and other malignancies as well as other nonmalignant immunopathologic disorders. Ifosfamide is a closely related analog. Skin rashes occur rarely and there are very rare reports of bullous rashes. It is not clear whether there is a different reaction rate between iv and PO. From 1976–1995, 22 cases of hypersensitivity reactions to iv cyclophosphamide were reported (38). These authors identified four of these cases at their institution over 2 yr, with 1204 total courses administered (0.003%). All 22 patients had symptoms compatible with an IgE reaction, ranging from urticaria to general-

ized life-threatening signs. Most occurred immediately; however, some did not start until 4–12 h later. In these latter cases, Popescu et al. demonstrated positive skin tests not to the parent drug, but to drug metabolites formed later (38). This may occur with other drugs, but the metabolites are not as well-defined.

Specific allergic reactions to ifosfamide have an incidence less than 1%. However, ifosfamide is usually given with mesnal to block the dose-related hemorrhagic cystitis, and specific allergic reactions to mesnal have been reported ranging from morbilliform and urticarial rashes to a systemic vasculitic-like syndrome, occurring after 3 wk of treatment (39). In one series of 15 patients with autoimmune disease treated with cyclophosphamide and mesnal, seven developed rashes and had positive skin prick, intradermal and/or patch tests only to mesnal (40), but no controls were done.

Cytarabine and Fludarabine

Cytarabine (also known as cytosine arabinoside) and fludarabine are antimetabolites used primarily to treat leukemias. Several unusual reactions are associated with cytarabine, including a syndrome of fever, chills, diaphoresis, myalgias, arthralgias, conjunctivitis, and macular-papular rashes, all coincident with administration. Many physicians treat with acetaminophen pre- and post-infusion. It is often administered as a continuous infusion for 3 d. Others are the development of palmar-planter erythema, with later desquamation and neutrophilic eccrine hidradenitis. None of these appear to be immunologically mediated; all are believed to be varied manifestations of the direct toxicity of the drug (5). Two cases of fatal TEN have been reported (41). Successful readministration in a child, 3 yr after several anaphylactoid reactions, has been reported (42).

Cytarabine is also available encapsulated in liposomes for intrathecal use. It may induce a chemical arachnoiditis, requiring concurrent treatment with dexamethasone. This is most likely a toxic reaction.

Dacarbazine

This is commonly used to treat Hodgkin's disease and multiple melanoma. There are infrequent reports of erythematous and urticarial rashes. Some patients develop fever to 39°C, with malaise and myalgias, after a large dose. This may last for several days, and may recur with further treatment. One case of anaphylaxis was reported in 1992 (5).

Dactinomycin

This has been available for 40 yr, and is currently used to treat choriocarcinoma and Wilms tumors. Hypersensitivity reactions are rare.

Fluorouracil

Fluorouracil is an antimetabolite most often used for the treatment of gastrointestinal and breast cancers. The hand-foot syndrome of rash is a frequent side effect of high-dose, short-term, and continuous infusions; this is considered a toxic rather than hypersensitivity side effect. In one study, 51% (36/70) developed symptoms after a median of nine courses (43). Most reactions were mild, and did not necessitate stopping the drug.

Hydroxyurea

It is indicated for squamous-cell carcinomas of the head and neck, as well as sickle-cell anemia. Hypersensitivity reactions are rare. There is a recent case report of hydroxyurea-induced pneumonitis (44).

Methotrexate

This has been used for 50 yr for multiple cancers and immune disorders. There are rare reports of anaphylaxis, urticaria, and hepatitis after several exposures. Two reports of associated anaphylaxis symptoms followed the first exposure (45).

Vincristine and Vinblastine

Vincristine is used to treat brain tumors, non-Hodgkin's lymphomas, and multiple

myeloma. Vinblastine is used for bladder cancer. Reactions to these drugs are very rare.

Other Modalities of Cancer Treatment

In addition to chemotherapeutic drugs, an increasing number of other modalities are now used to treat cancer. These include: hormone agonists and antagonists; immunomodulators such as interleukin-2 and interferon gamma; immune-stimulators such as bacillus Calmette-Guérin (BCG); monoclonal antibodies (MAbs) such as trastuzumab for breast cancer, and specific vaccines. These are discussed in detail in an accompanying article on biologic modifiers.

References

1. Drugs of Choice for Chemotherapy, in *The Medical Letter*, vol. 42, Abramowicz, M., ed., September 18, 2000, pp. 83–92.
2. Zanotti, K. M. and Markman, M. (2001), *Drug Saf.* **24**, 767–779.
3. Robinson, J. B., Singh, D., Bodurka-Bervers, D. C., Wharton, J. T., Gershenson, D. M., and Wolf, J. K. (2001), *Gynecol. Oncol.* **82**, 550–558.
4. Stone, H. D., DiPiro, C., Davis, P. C., Meyer, C. F., and Wray, B. B. (1998), *J. Allergy Clin. Immunol.* **101**, 429–431.
5. Weiss, R. B. (1992), *Sem. Oncol.* **19**, 458–477.
6. Larson, R. A., Fretzin, M. H., Dodge, R. K., and Schiffer, C. A. (1998), *Leukemia* **12**, 660–665.
7. Mueller, H. J., Beir, R., Loning, L., et al. (2001), *Br. J. Haematol.* **114**, 794–799.
8. *Physicians Desk Reference* 2001, Publishers Medical Economics, Montvale, NJ, p. 1928.
9. Woo, M. H., Storm, L. J., Sandlund, J. T., Ribeiro, R. C., et al. (2000), *J. Clin. Oncol.* **18**, 1525–1532.
10. Zanotti, K. M., Rybicki, L. A., Kennedy, A. W., Belinson, J. L., et al. (2001), *J. Clin. Oncol.* **19**, 3126–3129.
11. Polyzos, A., Tsavaris, N., Kosmas, C., Arnaouti, T., et al. (2001), *Oncology* **61**, 129–133.
12. Shukunami, K., Kurokawa, T., Kawakami, Y., Kubo, M., and Kotsuji, F. (1999), *Gynecol. Oncol.* **72**, 431–432.
13. Markman, M., Kennedy, A., Webster, K., Elson, P., et al. (1999), *J. Clin. Oncol.* **17**, 1141.
14. Goldberg, A., Confino-Cohen, R., Fishman, A., Beyth, Y., and Altaras, M. (1996), *J. Allergy Clin. Immunol.* **98**, 841–843.
15. Kellie, S. J., Crist, W. M., Pui, C. H., Crone, M. E., Fairclough, D. L., Rodman, J. H., et al. (1991), *Cancer* **67**, 1070–1075.
16. Hudson, M. N., Weinstein, H. J., Donaldson, S. S., Greewald, C., Kun, L., et al. (1993), *J. Clin. Oncol.* **11**, 1080–1084.

17. Szebeni, J., Alving, C. R., Savay, S., Barenholz, Y., et al. (2001), *Int. Immunopharmacol.* **1**, 721–735.
18. Nolte, H., Carstensen, H., and Hertz, H. (1988), *Am. J. Pediatr. Hematol. Oncol.* **10**, 308–312.
19. Hoetelmans, R. M., Schornagel, J. H., ten Bokkel Huinink, W. W., and Beijnen, J. H. (1996), *Ann. Pharmacother.* **30**, 367–371.
20. Grosen, E. (2000), *Lancet* **354**, 288–289.
21. Myers, J. (2000), *Clin. J. Oncol. Nurs.* **4**, 161–163.
22. Essayan, D. M., Kagey-Sobotka, A., Colarusso, P. J., Lichtenstein, L. M., Ozols, R. F., and King, E. D. (1996), *J. Allergy Clin. Immunol.* **97**, 42–46.
23. Kintzel, P. E. (2001), *Ann. Pharmacother.* **35**, 1114–1117.
24. Moon, C., Verschraegen, C. F., Bevers, M., Freedman, R., Kudelka, A. P., and Kavanagh, J. T. (2000), *Anticancer Drugs* **11**, 565–568.
25. Koppler, H., Heymans, J., and Weide, R. (2001), *Onkologie* **24**, 283–285.
26. Peereboom, D. M., Donehower, R. C., Eisenhauer, E. A., McGuire, W. P., et al. (1993), *J. Clin. Oncol.* **5**, 885–890.
27. Fishman, A., Gold, T., Goldberg, A., Confino-Cohen, R., et al. (1999), *Int. J. Gynecol. Cancer* **9**, 156–159.
28. Bernstein, B. J. (2000), *Ann. Pharmacother.* **11**, 1332–1335.
29. Fossella, F. V., Lee, J. S., Murphy, W. K., et al. (1994), *J. Clin. Oncol.* **12**, 1238–1244.
30. Coyle, T., Bushunow, P., Winfield, J., Wright, J., and Graziano, S. (1992), *Cancer* **15**, 2532–2540.
31. Giguere, J. K., Douglas, D. M., Lupton, G. P., Baker, J. R., and Weiss, R. B. (1988), *Med. Pediatr. Oncol.* **16**, 378–380.
32. Lehmann, D. F., Hurteau, T. E., Newman, N., Coyle, T. E. (1997), *Clin. Pharmacol. Ther.* **62**, 225–229.
33. Alberts, D. S. and Garcia, D. J. (1997), *Drugs* **54**, S30–S35.
34. Gabizon, A. A. (2001), *Cancer Investig.* **19**, 424–436.
35. Goram, A. L. and Richmond, P. L. (2001), *Pharmacotherapy* **6**, 751–763.
36. Korelitz, B. I., Zlantic, J., Goel, F., and Fuller, S. (1999), *J. Clin. Gastroenterol.* **28**, 341–344.
37. Torricelli, R., Kurer, S. B., Krtoner, T., and Wurtyrich, B. (1995), *Schweiz Med. Wochenschr.* **125**, 1870–1873.
- 37a. Cornwell, G. G., Pajak, T. F., and McIntyre, O. R., (1979), *Cancer Treat. Res.* **63**, 399–403.
38. Popescu, N. A., Sheehan, M. G., Kouides, P. A., et al. (1996), *J. Allergy Clin. Immunol.* **97**, 26–33.
39. Rheinhold-Keller, E., Mohr, J., Christophers, E., Nordmann, K., and Gross, W. L. (1992), *Clin. Investig.* **70**, 698–704.
40. Zonzits, E., Aberer, W., and Tappeiner, G. (1992), *Arch. Dermatol.* **128**, 80–82.
41. Ozkan, A., Apak, H., Celkan, T., Yuksel, L., Yildiz, I. (2001), *Pediatr. Dermatol.* **18**, 38–40.
42. Blanca, M., Torres, M. J., Giron, M., Corzo, J. L., and Martinez-Valverde, A. (1997), *Allergy* **52**, 1009–1011.
43. Chiara, S., Nobile, M. T., Barzacchi, C., et al. (1997), *Eur. J. Cancer* **33**, 967–969.
44. Sandhu, H. S., Barnes, P. J., and Hernandez, P. (2000), *Can. Resp. J.* **7**, 491–495.
45. Alkins, S. A., Byrd, J. C., Morgan, S. K., Ward, F. T., and Weiss, R. B. (1996), *Cancer* **15**, 2123–2126.