
CME review

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Diagnosis and management of hypersensitivity reactions related to common cancer chemotherapy agents

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Objectives: To review clinical hypersensitivity reactions related to common cancer chemotherapy agents and to discuss potential management strategies.

Data Sources: PubMed searches were performed for articles published from 1970 to 2008 regarding hypersensitivity to cancer chemotherapy and related agents using the keywords *hypersensitivity*, *allergy*, *chemotherapy*, *platinums*, *taxanes*, *asparaginase*, *epipodophyllotoxins*, and *procarbazine*. Retrieved articles were surveyed for additional citations.

Study Selection: Articles were reviewed for relevance to the subject matter, and the most pertinent articles were included in this review.

Results: Hypersensitivity reactions are commonly associated with the use of certain cancer chemotherapy drugs, including platinums, taxanes, asparaginase, procarbazine, and epipodophyllotoxins. Platinum agents (cisplatin, carboplatin, oxaliplatin) are associated with IgE-mediated hypersensitivity reactions, and skin testing may be indicated. Taxane (paclitaxel, docetaxel)-related reactions are generally non-IgE mediated, and premedication with corticosteroids and antihistamines is usually effective. Asparaginase has a high rate of hypersensitivity reactions that are likely IgE mediated or related to complement activation. Skin testing has been recommended but has not been validated for asparaginase. Procarbazine reactions can be IgE mediated but are also associated with a type III reaction manifested by pulmonary toxicity and cutaneous reactions. Hypersensitivity reactions related to epipodophyllotoxins may involve both immunologic and nonimmunologic factors that may be avoided with a slow infusion and premedication.

Conclusion: With the increasing use of cancer chemotherapy agents, hypersensitivity reactions are commonly encountered. Knowledge of the presentations of these reactions and management options give the treating physician the means to make an informed decision of how best to proceed.

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INTRODUCTION

Hypersensitivity reactions have been documented for most cancer chemotherapy. In the past decade the use of chemotherapy for neoplastic disease has increased significantly.

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Allergists are being consulted more often to assist in the management of these hypersensitivity reactions. The incidence of hypersensitivity reactions has been particularly significant with certain chemotherapeutic agents, including platinum compounds (cisplatin, carboplatin, oxaliplatin), taxanes (paclitaxel, docetaxel), L-asparaginase, epipodophyllotoxins (teniposide, etoposide), and procarbazine.¹ Reactions may be related to the parent compound, their metabolites, or the solvent. Manifestations of hypersensitivity reactions include rash, pruritus, bronchospasm, abdominal cramping, hypoten-

sion, and even death. Most severe chemotherapy-related reactions have the characteristics of an IgE-mediated mechanism, although others may act via direct mast cell or basophil degranulation or activation of the complement cascade. There have also been case reports of types II, III, and IV reactions.

A hypersensitivity reaction to a chemotherapeutic agent often poses a dilemma to the treating physician, who must consider discontinuing possible life-saving therapy vs the risk of a life-threatening anaphylactic/anaphylactoid reaction if chemotherapy is continued. Since hypersensitivity reactions can be severe, efforts directed at identifying patients at increased risk are crucial. Skin testing may be valuable in the evaluation of IgE-mediated chemotherapy reactions. However, skin testing is somewhat limited because of the lack of drug metabolites available for testing, unclear mechanisms responsible for reactions to certain drugs, and possible toxicity of testing reagents. To identify a hypersensitivity reaction, after administration of a drug, a tryptase level should be measured within the first few hours. Options to reduce the risk of continued therapy after a hypersensitivity reaction include changing drugs, desensitization, or premedication. The success of these various options vary, depending on the severity of the hypersensitivity reaction, the specific chemo-

therapeutic agent, and the hypothesized mechanism of action. This review aims to outline the most common presentations of hypersensitivity reactions associated with cancer chemotherapy agents and key aspects in the prevention and management of hypersensitivity reactions (Table 1).

CANCER CHEMOTHERAPY DRUGS COMMONLY RELATED TO HYPERSENSITIVITY REACTIONS

Carboplatin

Platinum-containing drugs have been reported to cause immediate-type hypersensitivity reactions and asthma in workers in the platinum-refining industry.² Hypersensitivity reactions have also been demonstrated in patients receiving platinum-based chemotherapy. Cisplatin was the first of the platinum drugs to be used. Carboplatin, an analog of cisplatin, has often been used in place of cisplatin because of a lower incidence of neurotoxicity, nephrotoxicity, and emetogenic potential.³ Carboplatin is particularly useful in the management of ovarian and lung cancer. However, like cisplatin, carboplatin has also been associated with hypersensitivity reactions.

Table 1. Common Presentations of Hypersensitivity Reactions Associated With Cancer Chemotherapy Agents and Key Aspects in the Prevention and Management of Hypersensitivity Reactions

Drug	Description of reaction	Prevention	Skin testing protocol	Future options after reaction
Carboplatin	Urticaria or angioedema, bronchospasm, hypotension, rash (mostly after cycles 6–8)	Skin testing after sixth course (validated)	Intradermal injection of 0.02 mL of undiluted aliquot from carboplatin preparation planned for infusion (100–240 µg)	Desensitization or substitute with cisplatin
Oxaliplatin	Urticaria or angioedema, bronchospasm, hypotension, rash, hemolytic anemia, idiosyncratic reactions (including cytokine release syndrome)	Skin testing reported to be 75%–80% accurate (not validated)		Desensitization
Paclitaxel	Urticaria or angioedema, bronchospasm, hypotension (commonly with first or second dose)	Premedication with antihistamines and corticosteroids		Desensitization in rare case that rechallenge causes another reaction or substitute with docetaxel
L-asparaginase	Urticaria or angioedema, bronchospasm, hypotension, rash (most occur after 2 weeks)	Skin testing proposed before first dose and anytime ≥1 wk between doses (not validated)	Intradermal injection of 0.1 mL of a 20-IU/mL dilution of asparaginase	Desensitization or substitute with different preparation (<i>Escherichia coli</i> , <i>Erwinia</i> , polyethylene glycol)
Procarbazine	Maculopapular rash, urticaria or angioedema, allergic alveolitis, toxic epidermal necrolysis, fixed drug reactions	No reliable means		Discontinue
Epipodophyllotoxins	Hypotension, dyspnea, bronchospasm	Slow infusion for 30–60 minutes		Rechallenge after premedication with antihistamines and steroids

Most hypersensitivity reactions to cisplatin and carboplatin are likely IgE mediated. The clinical manifestations of platinum-associated hypersensitivity reactions are typical of a type I hypersensitivity reaction and include urticaria, bronchospasm, rash, and hypotension.⁴ The number of courses of platinum chemotherapy before one observes the development of a reaction is also consistent with an immediate hypersensitivity reaction. Markman et al³ reported in a review of 205 patients that the mean number of courses of cisplatin or carboplatin before the demonstration of a hypersensitivity reaction was 8, whereas there was only a 1% incidence in patients receiving 6 or fewer courses. Sliesoraitis and Chikhale⁴ summarized 3 previous trials evaluating the cumulative risk of hypersensitivity in patients receiving carboplatin at different numbers of cycles. In patients receiving fewer than 5 cycles, there was less than a 1% incidence of a hypersensitivity reaction. The risk of hypersensitivity reactions increases significantly at cycle 6 and continues to increase to cycle 8 to a cumulative risk of 19.5%. A prolonged period of exposure (6 or more courses) is also typical of hypersensitivity reactions associated with cisplatin.⁵ However, there have been reported rare incidences of a reaction after a single large course.⁶

Because carboplatin is often administered together with paclitaxel, one must distinguish the hypersensitivity reactions associated with each. Carboplatin-associated hypersensitivity reactions vary greatly in clinical severity with more than 50% of reactions being moderate or severe, unlike paclitaxel hypersensitivity reactions, which tend to be more uniform and mild.^{3,7} Carboplatin hypersensitivity reactions also differ from paclitaxel in the time of the reaction with respect to the drug administration. Paclitaxel hypersensitivity reactions tend to manifest within the first few minutes of infusion, whereas carboplatin hypersensitivity reactions vary in timing from the first few minutes of drug administration to a few manifesting symptoms of a reaction days after drug administration.^{3,7} Paclitaxel-related reactions typically resolve rapidly after discontinuation of infusion. Severe reactions involving carboplatin often require several hours for symptoms to completely resolve.³

There is no standard protocol to prevent a carboplatin hypersensitivity reaction, but there are precautions that may be taken. To identify patients who may be at risk of a reaction, skin testing has been recommended for patients after the sixth course. Zanotti et al⁸ first showed that skin testing to carboplatin was able to identify patients who may safely be administered carboplatin with a 99% negative predictive value in a study involving 47 patients. The skin testing protocol consisted of an intradermal injection of 0.02 mL of an undiluted aliquot from the carboplatin preparation planned for infusion (100 to 240 μ g of carboplatin). Subsequently, they expanded this to 126 patients receiving more than 6 courses of platinum-based therapy and found a 98.5% negative predictive value, validating skin testing as a method to predict hypersensitivity reactions.⁹

Of concern is the patient who develops a reaction to carboplatin and requires further treatment. The physician must weigh the potential benefits of continuing therapy with the risk of a life-threatening reaction. Options available to the patient who has been skin test positive to carboplatin are desensitization, change from carboplatin to cisplatin, or discontinuation of platinum therapy.

Various desensitization protocols have been formulated to prevent the recurrence of a hypersensitivity reaction to carboplatin. These protocols have included prolonged infusion, escalating concentrations of infusion, and premedication. Successful desensitization to carboplatin has been reported in mostly small studies or case reports. Carboplatin desensitization has not been as consistently effective as for paclitaxel.^{3,6-8,10-15} However, recently, Castells et al¹⁵ reported a study of 413 cases of rapid desensitization to various chemotherapy agents, which included carboplatin (212 of the cases). Their 12-step protocol was safe and effective, with mild or no reactions in 94% of the total cases. The authors acknowledged that the limitation of their study was the bias toward females with certain types of cancer, and it is uncertain whether it may be successful in other populations. Further studies are needed before an optimal desensitization strategy can be defined. The treating physician must weigh the risk and benefits of desensitization because serious consequences, including death, have been reported after rechallenging patients with a platinum.^{7,10}

The success of the substitution of carboplatin with another platinum drug such as cisplatin is variable in preventing a hypersensitivity reaction. Some authors have been successful in replacing carboplatin with cisplatin if skin test results to the other agent are negative. Success of cisplatin substitution for carboplatin has been demonstrated in a few case reports and clinical studies.^{16,17} Jones et al¹⁷ described 5 patients with previous hypersensitivity to carboplatin who were subsequently given cisplatin after a full cisplatin desensitization protocol. All patients tolerated cisplatin with this desensitization protocol. However, when a subsequent shortened protocol of desensitization was attempted, 2 patients terminated treatment with cisplatin because of the development of hypersensitivity reactions. There are reports of serious consequences from cross-reactivity, with 1 report of death.¹⁰ Because of the limited number of studies, the true incidence of cross-hypersensitivity of cisplatin and carboplatin has yet to be defined.

Oxaliplatin

Oxaliplatin is a third-generation platinum compound that has been used in combination with fluorouracil in the treatment of colorectal cancer and a variety of other malignancies, such as advanced ovarian carcinoma, breast cancer, non-Hodgkin lymphoma, melanoma, non-small cell lung cancer, and head and neck malignancies.¹⁸ Oxaliplatin, like other platinum agents, is associated with hypersensitivity reactions.

Hypersensitivity reactions associated with oxaliplatin are often unpredictable but are rarely life-threatening. The inci-

dence of severe hypersensitivity reactions to oxaliplatin is approximately 0.5%, whereas the overall hypersensitivity rate is 13% (with most reactions being mild).¹⁹ However, the incidence of hypersensitivity reactions is increasing as a result of increasing use in both adjuvant and metastatic treatment of colorectal cancer. Hypersensitivity reactions to oxaliplatin include rash, urticaria, angioedema, bronchospasm, and rarely hypotension.^{18,20} Only a few incidences of severe hypersensitivity reactions to oxaliplatin manifested as anaphylaxis are reported in case reports.^{22,23}

The mechanism responsible for hypersensitivity reactions to oxaliplatin seems to be IgE mediated, like that of other platinum-based chemotherapeutic agents. Herrero et al²⁴ suggest that an IgE-mediated mechanism of hypersensitivity is supported by findings that reactions occur after several courses of therapy, symptoms usually present in the first 60 minutes of the infusion, and the results of skin tests are usually positive. In another study,²⁰ 13% of patients developed hypersensitivity reactions minutes after the start of oxaliplatin infusion, after 2 to 17 exposures (mean, 9.4), but none experienced reactions after the first infusion.

Pretreatment regimens with antihistamines and corticosteroids to prevent recurrent hypersensitivity reactions from oxaliplatin have not been reliable.^{20,21,25,26} Brandi et al²⁰ showed in their study that prophylaxis with high-dose steroids and antihistaminic drugs for several days before the infusion of oxaliplatin was not successful in preventing hypersensitivity reactions. Five of 6 patients given prophylaxis before drug infusion subsequently developed another hypersensitivity reaction of comparable intensity as the first. Thomas et al²⁵ and Bhargava et al²⁶ both described cases in which, similarly, prophylaxis failed to prevent a hypersensitivity reaction. Patients with mild to moderate hypersensitivity reactions to oxaliplatin may be able to tolerate rechallenge with appropriate prophylaxis. However, those experiencing severe hypersensitivity reactions are unlikely to benefit from a prophylactic regimen and will likely have recurrence of a similar reaction.²⁵

Skin testing as a method of predicting hypersensitivity reactions to oxaliplatin has been studied in only a small population of patients, and its use is not validated. Skin prick tests are not useful because the results are usually negative. Studies examining intradermal oxaliplatin tests have not provided consistent results.^{24,27–29} Although a positive skin test result may be helpful, a negative test result does not exclude the possibility of a future hypersensitivity reaction. Meyer et al²⁸ and Garufi et al²⁷ estimate that skin testing for oxaliplatin is approximately 75% to 80% accurate.

Successful desensitization protocols consisting of a prolonged infusion or escalating concentrations of oxaliplatin have been studied by different authors and may prove to be valuable in patients requiring oxaliplatin therapy. However, an optimal protocol needs further inquiry because successful cases of desensitization have been demonstrated on a small number of individuals.^{13,15,24,28,30,31}

Although most reactions to oxaliplatin seem to be IgE mediated, type II hypersensitivity and delayed idiosyncratic reactions have been reported. Type II reactions occur in which oxaliplatin leads to hemolytic anemia.³² An idiosyncratic reaction was described by Thomas et al²⁵ in which a patient developed fevers, rigors, and chest tightness several hours after the completion of infusion. de Vries et al³³ described a patient who developed severe respiratory symptoms consisting of stridor, dyspnea, and oxygen desaturation approximately 24 hours after completion of oxaliplatin infusion. Santini et al³⁴ described a patient who developed abdominal cramps, diarrhea, and fevers 20 minutes after completion of infusion with associated interleukin 6 and tumor necrosis factor α elevation, possibly due to a cytokine release syndrome with oxaliplatin acting as a superantigen. Tonini et al³⁵ described 5 cases similar to that reported by Santini et al.

Taxanes (Paclitaxel and Docetaxel)

Paclitaxel is a chemotherapeutic agent commonly used in various gynecologic, breast, and non–small cell lung cancers. Docetaxel is a newer semisynthetic taxane.

Hypersensitivity reactions are common with paclitaxel, occurring in up to 30% of patients in some early studies. Most manifest symptoms typical of type I hypersensitivity reactions, including bronchospasm, urticaria, and hypotension.³⁶ Subsequent studies³⁷ have shown that premedication with antihistamines and corticosteroids have decreased the incidence of severe hypersensitivity reactions to approximately 2% to 4%. Most severe reactions occur within the first few minutes of paclitaxel administration, usually after the first or second dose. In a review of 25 patients,³⁸ 78% developed reactions within the first 10 minutes of paclitaxel infusion. In this same study, 56% of the reactions were found to occur during the first taxol dose and 40% during the second dose.

Hypersensitivity reactions related to paclitaxel are thought to be non-IgE mediated because most reactions occur with the first dose. Although it is still controversial whether the solvent, Cremophor EL, or the taxane moiety is responsible for hypersensitivity reactions, most studies implicate Cremophor EL. Cremophor is thought to be at least partially responsible for the hypersensitivity reactions because it has been shown to induce histamine release and also because other drugs formulated in Cremophor EL, such as vitamin K and cyclosporine, have similar adverse effects.³⁸ Of note, a novel Cremophor EL-free albumin-bound paclitaxel (Abraxane) has not produced significant hypersensitivity reactions in phase 1, 2, or 3 studies, despite absence of premedication.³⁹ During postmarketing surveillance, rare incidences of severe hypersensitivity reactions to Abraxane have been reported.

Premedication with corticosteroids and antihistamines has been effective for paclitaxel treatment, reducing hypersensitivity reactions to approximately 2% to 4% of cases.³⁷ Currently, premedication for paclitaxel hypersensitivity includes dexamethasone, 20 mg orally or intravenously 12 and 6 hours before drug infusion, diphenhydramine, 50 mg, and cimetidine.

dine, 300 mg, or ranitidine, 50 mg, both intravenously 30 minutes before treatment.

A few trials suggest that giving prophylactic intravenous steroids 30 minutes before chemotherapy infusion may be a more convenient and as effective prophylaxis strategy as giving oral steroids 12 and 6 hours before chemotherapy.^{40,41} However, Kwon et al⁴² showed that the prophylactic regimen of intravenous dexamethasone in addition to antihistamines, given 30 minutes before paclitaxel, was associated with a higher rate of hypersensitivity reactions compared with the standard regimen of oral dexamethasone given 12 and 6 hours and antihistamines given 30 to 60 minutes before paclitaxel (17.3% vs 7.5%).

Early phase 1 data suggested that slower administration rates and longer duration infusions were associated with fewer hypersensitivity reactions.³⁷ However, with effective premedication regimens prolonged infusions may not be necessary. Eisenhauer et al⁴³ evaluated the incidence of hypersensitivity reactions among women with relapsed ovarian cancer who were randomized to high- vs low-dose (135 and 175 mg per square meter of body surface area) and long vs short (3-hour and 24-hour) infusion of paclitaxel. The overall incidence of hypersensitivity reactions was found to be similar for the 3-hour (2.1%) and 24-hour (1.0%) infusion protocols.

Most patients demonstrating hypersensitivity reactions can be successfully re-treated with paclitaxel. Olsen et al⁴⁴ demonstrated that most patients can be re-treated with paclitaxel within the same day. Markman et al⁴⁵ also explored the feasibility to re-treat patients with hypersensitivity reactions with paclitaxel. They reported that if the infusion of paclitaxel was reinitiated 30 minutes after an initial reaction, in 65 of the 70 episodes (93%) the patients were able to complete the infusion without the subsequent development of a second reaction. Although the mechanism is unclear, they hypothesized that the initial reaction depleted the relevant mediators of hypersensitivity, which thereafter required time to recover sufficiently to produce a subsequent reaction.⁴⁶

In the rare situation where the patient develops another reaction after rechallenge with paclitaxel, various successful desensitization protocols have been developed.^{15,45,46} In a study by Feldweg et al,⁴⁷ the authors described 17 patients who received 77 total taxane cycles and were desensitized to either docetaxel or paclitaxel using a 6- to 7-hour protocol. Seventy-two patients tolerated taxane therapy, whereas 4 patients developed minor hypersensitivity reactions that were much less severe than their initial reaction. In the recent study by Castells et al,¹⁵ the authors described 140 successful paclitaxel desensitizations.

Another alternative in patients experiencing a severe hypersensitivity reaction to paclitaxel is its substitution with docetaxel. Data have been inconsistent on the cross-reactivity of these 2 agents. Two clinical trials demonstrated successful treatment with docetaxel after hypersensitivity reactions to paclitaxel.^{48,49} However, Dizon et al⁵⁰ recently recommended that if docetaxel is substituted for paclitaxel, caution must be

exercised, because their study showed a cross-reactivity rate of 90% even though docetaxel is formulated with polysorbate 80 instead of Cremophor EL, suggesting that the taxane moiety may be responsible for cross-reactivity.

Hypersensitivity reactions were expected to be lower with docetaxel compared with paclitaxel because of its formulation in the solvent polysorbate 80 not Cremophor EL. However, docetaxel caused hypersensitivity reactions in up to 30% of patients treated without premedication.⁵¹ With premedication, the risk of serious reactions was decreased to 2% of patients, and treatment rarely needed to be discontinued. Like paclitaxel, the hypersensitivity reaction was thought to be non-IgE mediated because most reactions occur with the first 2 doses. The mechanism is unknown.⁵² The premedication regimen for docetaxel is different from that for paclitaxel. Patients receiving docetaxel require dexamethasone, 16 mg/d (8 mg twice daily) for 3 days starting 1 day before administration, whereas those receiving paclitaxel are given dexamethasone, 20 mg at 12 and 6 hours before administration, combined with diphenhydramine, 50 mg, and cimetidine, 300 mg, or ranitidine, 50 mg, both given intravenously 30 to 60 minutes before administration.

In addition to hypersensitivity reactions, docetaxel is also associated with fluid retention, including peripheral edema, ascites, and pleural effusion, which appears to be related to capillary leakage, and is dose related.^{52,53} The incidence of this adverse effect is delayed with corticosteroids.⁵⁴

Asparaginase

L-asparaginase is an enzyme used in the treatment of acute lymphocytic leukemia and is the chemotherapeutic agent associated with the highest rate of hypersensitivity reactions.⁵ L-asparaginase is available in 3 forms: an *Escherichia coli* derivative, Elspar; an *Erwinia chrysanthemi* derivative, *Erwinia carotovora*; and a polyethylene glycol attached form, pegasparagase (Oncaspar).⁵⁵ The incidence of hypersensitivity reactions has been variable, depending on the route of administration and dosing, but these reactions have been reported to occur in up to 35% of treated patients,⁵⁶ although serious anaphylactic reactions occur in less than 10% of patients.⁵⁷ Hypersensitivity has been reported even after the first dose but is more common the greater the number of doses previously administered. Most reactions occur after 2 weeks of either daily or 3 times per week dosing⁵⁸ and usually manifest within 1 hour of administration.⁵ Symptoms of hypersensitivity may include urticaria, rash, abdominal pain, bronchospasm, hypotension, and death.⁵

The mechanism of hypersensitivity to L-asparaginase is incompletely understood but may be either IgE mediated or related to complement activation. Khan and Hill⁵⁹ showed in a study of 5 patients who developed a hypersensitivity reaction that the mechanism was IgE mediated by means of skin testing and Prausnitz-Kiustner reaction studies. In a study by Fabry et al,⁶⁰ the authors showed that complement activation mediated by IgG or IgM complexes with L-asparaginase may be responsible for hypersensitivity reactions to L-asparaginase.

Several risk factors have been associated with a higher rate of hypersensitivity reactions to L-asparaginase. Intravenous administration of L-asparaginase is associated with higher rates of hypersensitivity than intramuscular administration. Thus, L-asparaginase is now almost always given intramuscularly or subcutaneously.¹ Evans et al⁵⁷ showed that patients who were not being treated with a combination of L-asparaginase, vincristine, and prednisone but rather L-asparaginase alone had higher rates of hypersensitivity. Patients who are administered L-asparaginase at weekly or longer intervals compared with daily dosing have an increased rate of hypersensitivity reactions.⁵⁷ Likewise, prior exposure to L-asparaginase months or even several years earlier also increases the rate of hypersensitivity reactions. Albo et al⁶¹ showed in 92 patients previously treated with L-asparaginase 3 years ago without hypersensitivity reactions who now underwent consolidation therapy that 35% had hypersensitivity reactions. Mueller et al⁶² recently also showed that re-treatment is associated with higher rates of hypersensitivity. In his study, 24% of 76 children with acute lymphocytic leukemia developed hypersensitivity reactions during reinduction treatment.

Because of the high rates of hypersensitivity reactions, skin testing and administration of a test dose have been proposed. Some recommend skin testing before the first dose and any time thereafter if an interval of 1 week or greater has passed between doses.¹ The recommendation is 0.1 mL intradermally of a 20-IU/mL dilution of drug.¹ However, this testing is not standardized, and both false-positive and false-negative results have been documented.¹ Test doses of L-asparaginase may also be of limited value because the small doses rarely produce a reaction and often produce false-negative results.⁵⁷ Therefore, any time L-asparaginase is administered, one must be prepared to respond promptly to a hypersensitivity reaction.

There are several options in the treatment of a patient who develops a hypersensitivity reaction to L-asparaginase who needs to continue treatment. Desensitization is an option in patients who develop a hypersensitivity reaction or have a positive skin test result. Another option is to switch the patient to a different preparation of L-asparaginase. L-asparaginase is derived from 2 antigenically distinct preparations: *E coli* or *Erwinia*, a parasitic bacteria. Beard et al⁶³ were the first to switch a patient who developed a hypersensitivity reaction from *E coli*-derived to *Erwinia*-derived L-asparaginase. In a study, 21 patients who had severe hypersensitivity reactions to *E coli*-derived L-asparaginase were switched to *Erwinia*-derived L-asparaginase, and 18 of 20 were able to tolerate the treatment.⁶⁴ However, cross-reactivity has been reported to occur after the first dose of *Erwinia*-derived L-asparaginase, or the patient may develop antibodies to it after subsequent doses and potentially have anaphylaxis.⁶⁵ The final option is to substitute L-asparaginase with pegaspargase, which is asparaginase that is covalently attached to polyethylene glycol. Pegaspargase is less immunogenic than L-asparaginase, and when used in patients with previous reactions to the native drug, 70% of patients tolerate intramuscular pegaspargase, whereas 40% tolerate the intravenous

form.¹ Pegaspargase may be of value in patients who are sensitive to both *E coli*-derived and *Erwinia*-derived L-asparaginase.⁶⁶ However, there is a risk in giving a drug of prolonged duration should an allergic reaction occur.

Procarbazine

Procarbazine is an oral chemotherapeutic agent used in the treatment of Hodgkin disease and brain malignancies and is associated with various types of hypersensitivity reactions. These reactions include type I hypersensitivity reactions, rarely type III reactions manifested by allergic alveolitis, and other cutaneous reactions, including toxic epidermal necrolysis and fixed drug reactions.

The most common cutaneous reaction to procarbazine is a maculopapular rash, but occasionally manifests as a type I reaction represented by urticaria or angioedema as well.⁵ The incidence of type I reactions is higher among patients receiving procarbazine for the treatment of brain malignancies in comparison to Hodgkin disease or other solid tumors.^{67,68} Procarbazine-associated hypersensitivity reactions may be higher in patients with brain malignancies because of the concomitant use of anticonvulsants, such as phenytoin, phenobarbital, or carbamazepine. These anticonvulsants lead to increased conversion of procarbazine into cytotoxic metabolites.⁶⁸

Hypersensitivity to procarbazine may also rarely present as a type III reaction manifested by pulmonary toxicity.^{69,70} Patients with this type of hypersensitivity reaction typically present with cough and dyspnea most commonly during or after the second cycle. Evaluation often reveals interstitial pneumonitis, restriction on pulmonary function tests, and sometimes prominent eosinophilia.⁷⁰ Discontinuation of procarbazine and corticosteroid treatment may improve symptoms.

Hypersensitivity reactions associated with procarbazine therapy are difficult to predict, and there is no reliable means to prevent their occurrence. Rechallenge invariably leads to recurrence of symptoms or sometimes life-threatening adverse outcomes^{67,69}; thus, therapy should be discontinued.

Epipodophyllotoxins (*Etoposide and Teniposide*)

The epipodophyllotoxins, etoposide and teniposide, are antimitotic agents that are occasionally associated with hypersensitivity reactions. Etoposide is used in the treatment of refractory testicular tumors and small cell lung cancer and is available in intravenous and oral formulations. Teniposide is used to treat hematologic and neurologic malignancies and only available in the intravenous formulation. Etoposide and teniposide are associated with a 6% to 41% incidence of hypersensitivity reactions and a 0.7% to 14% incidence of anaphylaxis.^{71,72} Teniposide is more commonly associated with reactions than etoposide. Although reactions may be manifested by hypotension, dyspnea, and bronchospasm, most are of low-grade severity.^{73,74} However, severe hypotension is often seen when the drug is infused too rapidly.⁷³

The mechanism responsible for hypersensitivity reactions associated with the epipodophyllotoxins is unclear but may

include both immunologic and nonimmunologic mechanisms. Reactions often occur within the first few minutes of drug infusion but can also occur hours after administration.⁵ Symptoms have been reported to occur after the first infusion but more commonly after multiple doses. Reactions during the first dose are suggestive of a nonimmunologic mechanism, whereas reactions seen after several doses are more consistent with the development of an antibody-mediated reaction. In a study by Kellie et al,⁷² patients with acute leukemia were treated with high cumulative doses of teniposide, and it was noted that hypersensitivity reactions became more likely as the cumulative dose increased.

It is also unclear whether hypersensitivity reactions are associated with the compound itself or the solvent in which it is diluted. Teniposide is dissolved in Cremophor, the same diluent as paclitaxel. Intravenous etoposide is dissolved in polysorbate (Tween) 80. Oral etoposide is not associated with hypersensitivity reactions, supporting the idea that the solvent may be responsible.⁵ Etoposide phosphate, a structurally related compound to intravenous etoposide, is highly soluble in aqueous solution, and thus no solvent is needed. Early trials showing that hypersensitivity reactions are lower with etoposide phosphate compared with intravenous etoposide suggest an etiologic role of the solvent in reactions.⁷⁵ Although the solvents have been associated with hypersensitivity reactions, the epipodophyllotoxins themselves may be responsible. Nolte et al⁷⁶ demonstrated that when sensitized individuals were exposed to both teniposide and Cremophor EL, teniposide degranulated basophils, whereas Cremophor EL failed to do so. Cross-sensitivity has also been reported to occur between etoposide and teniposide, despite being dissolved in different solvents.⁷⁷

Hypersensitivity reactions involving intravenous epipodophyllotoxins may be prevented with slow infusion and are usually successfully managed with corticosteroids and antihistamines if a reaction were to develop. Rapid infusion with intravenous epipodophyllotoxins is commonly associated with hypotension; thus, it is recommended that infusions take place for more than 30 to 60 minutes.¹ Patients developing a hypersensitivity reaction are usually successfully rechallenged with a prophylactic regimen of corticosteroids and antihistamines.^{72,78,79} Hudson et al⁷⁸ reported in their study that 78% of patients were rechallenged successfully to intravenous etoposide. Treatment with etoposide phosphate may be successful in patients who develop recurrent reactions to intravenous etoposide despite premedication.⁷⁹

CONCLUSION

Hypersensitivity reactions have been observed during therapy with most cancer chemotherapy agents. As the use of chemotherapy continues to increase, education regarding diagnosis and management of adverse reactions becomes vital, assisting in the decision to discontinue vs rechallenge with the implicated drug. Chemotherapy agents most commonly associated with hypersensitivity reactions include the platinum (cisplatin, carboplatin, oxaliplatin), taxanes (paclitaxel,

docetaxel), asparaginase, procarbazine, and epipodophyllotoxins (teniposide, etoposide). The mechanisms underlying most of these hypersensitivity reactions are unclear and may include type I, II, III, and IV hypersensitivity reactions or anaphylactoid reactions involving nonspecific mast cell mediator release. Physicians involved in the treatment of these patients must be familiar with reactions associated with a particular agent. The management of hypersensitivity reactions can be improved with the appropriate use of the various options: skin testing, premedication, replacement with another agent, and desensitization.

REFERENCES

1. Shepherd GM. Hypersensitivity reactions to chemotherapeutic drugs. *Clin Rev Allergy Immunol*. 2003;24:253-262.
2. Cleare MK, Hughes EG, Jacoby B, Pepys J. Immediate (type I) allergic responses to platinum compounds. *Clin Allergy*. 1976;6:183-195.
3. Markman M, Kennedy A, Webster K, et al. Clinical features of hypersensitivity reactions to carboplatin. *J Clin Oncol*. 1999;17:1141-1145.
4. Sliesoraitis S, Chikhale PJ. Carboplatin hypersensitivity. *Int J Gynecol Cancer*. 2005;15:13-18.
5. Weiss RB. Hypersensitivity reactions. *Semin Oncol*. 1992;19:458-477.
6. Kook H, Kim KM, Choi SH, et al. Life-threatening carboplatin hypersensitivity during conditioning for autologous PBSC transplantation: successful rechallenge after desensitization. *Bone Marrow Transplant*. 1998;21:727-729.
7. Zweig S, Roman LD, Mderspach LI. Death from anaphylaxis to cisplatin: a case report. *Gynecol Oncol*. 1994;53:121-122.
8. Zanotti KM, Rybicki LA, Kennedy AW, et al. Carboplatin skin testing: a skin-testing protocol for predicting hypersensitivity to carboplatin chemotherapy. *J Clin Oncol*. 2001;19:3126-3129.
9. Markman M, Zanotti K, Peterson G, Kulp B, Webster K, Belinson J. Expanded experience with an intradermal skin test to predict for the presence or absence of carboplatin hypersensitivity. *J Clin Oncol*. 2003;21:4611-4614.
10. Dizon DS, Sabbatini PJ, Aghajanian C, Hensley ML, Spriggs DR. Analysis of patients with epithelial ovarian cancer or fallopian tube carcinoma retreated with cisplatin after the development of a carboplatin allergy. *Gynecol Oncol*. 2002;84:378-382.
11. Rose PG, Fusco N, Smrekar M, Mossbruger K, Rodriguez M. Successful administration of carboplatin in patients with clinically documented carboplatin hypersensitivity. *Gynecol Oncol*. 2003;89:429-433.
12. Choi J, Harnett P, Fulcher DA. Carboplatin desensitization. *Ann Allergy Asthma Immunol*. 2004;93:137-141.
13. Markman M, Hsieh F, Zanotti K, et al. Initial experience with a novel desensitization strategy for carboplatin-associated hypersensitivity reactions: carboplatin-hypersensitivity reactions. *J Cancer Res Clin Oncol*. 2004;130:25-28.
14. Confino-Cohen R, Fishman A, Altaras M, Goldberg A. Successful carboplatin desensitization in patients with proven carboplatin allergy. *Cancer*. 2005;104:640-643.
15. Castells MC, Tennant NM, Sloane DE, et al. Hypersensitivity reactions to chemotherapy: outcomes and safety of rapid desensitizations in 413 cases. *J Allergy Clin Immunol*. 2008;122:574-580.
16. Ottiano A, Tambaro R, Greggi S, et al. Safety of cisplatin after severe hypersensitivity reactions to carboplatin in patients with recurrent ovarian carcinoma. *Anticancer Res*. 2003;23:3465-3468.
17. Jones R, Ryan M, Friedlander M. Carboplatin hypersensitivity reactions: re-treatment with cisplatin desensitization. *Gynecol Oncol*. 2003;89:112-115.
18. Gowda A, Goel R, Berdzik J, Leichman CG, Javle M. Hypersensitivity reactions to oxaliplatin: incidence and management. *Oncology*. 2004;18:1671-1674.
19. Oxaliplatin [package insert].
20. Brandi G, Pantaleo MA, Galli C, et al. Hypersensitivity reactions related

- to oxaliplatin (OHP). *Br J Cancer*. 2003;89:477–481.
21. Maindault-Goebel F, Tournigand C, et al. Allergic-type reactions to oxaliplatin: retrospective analysis of 42 patients. *Eur J Cancer*. 2005; 41:2262–2267.
 22. Tournigand C, Maindault-Goebel F, Louvet C, de Gramont A, Krulik M. Severe anaphylactic reactions to oxaliplatin. *Eur J Cancer*. 1998;34: 1298–1299.
 23. Medioni J, Coulon MA, Morere JF, Hennebelle F, Piperno-Neumann S, Breau JL. Anaphylaxis after oxaliplatin. *Ann Oncol*. 1999;10:610.
 24. Herrero T, Tornero P, Infante S, et al. Diagnosis and management of hypersensitivity reactions caused by oxaliplatin. *J Invest Allergol Clin Immunol*. 2006;16:327–330.
 25. Thomas RR, Quinn MG, Schuler B, Grem JL. Hypersensitivity and idiosyncratic reactions to oxaliplatin. *Cancer*. 2003;97:2301–2307.
 26. Bhargava P, Gammon D. Hypersensitivity and idiosyncratic reactions to oxaliplatin. *Cancer*. 2004;100:211–212.
 27. Garufi C, Cristaudo A, Vanni B, et al. Skin testing and hypersensitivity reactions to oxaliplatin. *Ann Oncol*. 2003;14:497–502.
 28. Meyer L, Zuberbier T, Worm M, Oettle H, Riess H. Hypersensitivity reactions to oxaliplatin: cross-reactivity to carboplatin and the introduction of a desensitization schedule. *J Clin Oncol*. 2002;20:1146–1147.
 29. Pagani M, Bonadonna P, Senna GE, Antico A. Standardization of skin tests for diagnosis and prevention of hypersensitivity reactions to oxaliplatin. *Int Arch Allergy Immunol*. 2008;145:54–57.
 30. Mis L, Fernando NH, Hurwitz HI, Morse MA. Successful desensitization to oxaliplatin. *Ann Pharmacother*. 2005;39:966–969.
 31. Gammon D, Bhargava P, McCormick MJ. Hypersensitivity reactions to oxaliplatin and the application of a desensitization protocol. *Oncologist*. 2004;9:546–549.
 32. Garufi C, Vaglio S, Brienza S, et al. Immunohemolytic anemia following oxaliplatin administration. *Ann Oncol*. 2000;11:497.
 33. de Vries RS, Mattijssen EJ, van Sorge AA. Serious delayed hypersensitivity reaction to oxaliplatin. *Ann Oncol*. 2004;17:1723–1724.
 34. Santini D, Tonini G, Salerno A, et al. Idiosyncratic reaction after oxaliplatin infusion. *Ann Oncol*. 2001;12:132–133.
 35. Tonini G, Santini D, Vincenzi B, et al. Oxaliplatin may induce cytokine-release syndrome in colorectal cancer patients. *J Biol Regul Homeost Agents*. 2002;16:105–109.
 36. Rowinsky EK, Donehower RC. Paclitaxel (Taxol). *N Engl J Med*. 1995;332:1004–1014.
 37. Taxol (paclitaxel) injection [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; March 2003.
 38. Weiss RB, Donehower RC, Wiernik PH, et al. Hypersensitivity reactions from taxol. *J Clin Oncol*. 1990;8:1263–1268.
 39. Gradishar WJ, Tjulandin S, Davidson N, et al. Phase III trial of nanoparticle albumin-bound paclitaxel compared with polyethylated castor oil-based paclitaxel in women with breast cancer. *J Clin Oncol*. 2005; 23:7794.
 40. Bookman MA, Kloth DD, Kover PE, Smolinski S, Ozols RF. Short-course intravenous prophylaxis for paclitaxel-related hypersensitivity reactions. *Ann Oncol*. 1997;8:611–614.
 41. Markman M, Kennedy A, Webster K, Peterson G, Kulp B, Belinson J. An effective and more convenient drug regimen for prophylaxis against paclitaxel-associated hypersensitivity reactions. *J Cancer Res Clin Oncol*. 1999;125:427–429.
 42. Kwon JS, Elit L, Finn M, et al. A comparison of two prophylactic regimens for hypersensitivity reactions to paclitaxel. *Gynecol Oncol*. 2002;84:420–425.
 43. Eisenhauer EA, ten Bokkel Huinink WW, Swenerton KD, et al. European-Canadian randomized trial of paclitaxel in relapsed ovarian cancer: high-dose versus low-dose and long versus short infusion. *J Clin Oncol*. 1994;12:2654–2666.
 44. Olson JK, Sood AK, Sorosky JJ, Anderson B, Buller RE. Taxol hypersensitivity: rapid retreatment is safe and cost effective. *Gynecol Oncol*. 1998;68:25–28.
 45. Markman M, Kennedy A, Webster K, Kulp B, Peterson G, Belinson J. Paclitaxel-associated hypersensitivity reactions: experience of the gynecologic oncology program of the Cleveland Clinic Cancer Center. *J Clin Oncol*. 2000;18:102–105.
 46. Markman M. Managing taxane toxicities. *Support Care Cancer*. 2003; 11:144–147.
 47. Feldweg AM, Lee CW, Matulonis UA, Castells M. Rapid desensitization for hypersensitivity reactions to paclitaxel and docetaxel: a new standard protocol used in 77 successful treatments. *Gynecol Oncol*. 2005;96:824–829.
 48. Lokich J, Anderson N. Paclitaxel hypersensitivity reactions: a role for docetaxel substitution. *Ann Oncol*. 1998;9:573–574.
 49. Moon C, Verschraegen CF, Bevers M, Freedman R, Kudelka AP, Kavanagh JJ. Use of docetaxel (Taxotere) in patients with paclitaxel (Taxol) hypersensitivity. *Anticancer Drugs*. 2000;11:565–568.
 50. Dizon DS, Schwartz J, Rojan A, et al. Cross-sensitivity between paclitaxel and docetaxel in a women's cancers program. *Gynecol Oncol*. 2006;100:149–151.
 51. Schrijvers D, Wanders J, Dirix L, et al. Coping with toxicities of docetaxel (Taxotere). *Ann Oncol*. 1993;4:610–611.
 52. Ardavanis A, Tryfonopoulos D, Yiotis I, Gerasimidis G, Baziotis N, Rigatos G. Non-allergic nature of docetaxel-induced acute hypersensitivity reactions. *Anticancer Drugs*. 2004;15:581–585.
 53. Semb KA, Aamdal S, Oian P. Capillary protein leak syndrome appears to explain fluid retention in cancer patients who receive docetaxel treatment. *J Clin Oncol*. 1998;16:3426–3432.
 54. Piccart MJ, Klijn J, Paridaens R, et al. Corticosteroids significantly delay the onset of docetaxel-induced fluid retention: final results of a randomized study of the European Organization for Research and Treatment of Cancer Investigational Drug Branch for Breast Cancer. *J Clin Oncol*. 1997;15:3149–3155.
 55. Asselin BL. The three asparaginases: comparative pharmacology and optimal use in childhood leukemia. *Adv Exp Med Biol*. 1999;457: 621–629.
 56. Dellinger CT, Miale TD. Comparison of anaphylactic reactions to asparaginase derived from *Escherichia Coli* and from *Erwinia* cultures. *Cancer*. 1976;38:1843–1846.
 57. Evans WE, Tsiatis A, Rivera G, et al. Anaphylactoid reactions to *Escherichia coli* and *Erwinia asparaginase* in children with leukemia and lymphoma. *Cancer*. 1982;49:1378–1383.
 58. Weiss RB, Bruno S. Hypersensitivity reactions to cancer chemotherapeutic agents. *Ann Intern Med*. 1981;94:66–72.
 59. Khan A, Hill JM. Atopic hypersensitivity to L-asparaginase: resistance to immunosuppression. *Int Arch Allergy Appl Immunol*. 1971;40:463–469.
 60. Fabry U, Korholz D, Jurgens H, Gobel U, Wahn V. Anaphylaxis to L-asparaginase during treatment for acute lymphoblastic leukemia in children-evidence of a complement-mediated mechanism. *Pediatr Res*. 1985;19:400–408.
 61. Albo V, Miller D, Leiken S, et al. Toxicity experience with a second course of *E. coli* L-asparaginase (L-asp) therapy 3 years after induction course in children with acute lymphoblastic leukemia (ALL) in continuous remission. *Proc Am Soc Clin Oncol*. 1983;2:abstract.
 62. Muller H, Beier R, Löning L, et al. Pharmacokinetics of native *Escherichia coli* asparaginase (Asparaginase medac) and hypersensitivity reactions in ALL-BFM 95 reinduction treatment. *Br J Haematol*. 2001; 114:794–799.
 63. Beard MEJ, Crowther D, Galton DA, et al. L-asparaginase in treatment of acute leukaemia and lymphosarcoma. *BMJ*. 1970;1:191–195.
 64. Larson RA, Fretzin MH, Dodge RK, Schiffer CA. Hypersensitivity reactions to L-asparaginase do not impact on the remission duration of adults with acute lymphoblastic leukemia. *Leukemia*. 1998;12:660–665.
 65. Clavell LA, Gelber RD, Cohen HJ, et al. Four-agent induction and intensive asparaginase therapy for treatment of childhood acute lymphoblastic leukemia. *N Engl J Med*. 1986;315:657–663.
 66. Holle LM. Pegasparagase: an alternative. *Ann Pharmacother*. 1997;31: 616–624.
 67. Coyle T, Bushnow P, Winfield J, Wright J, Graziano S. Hypersensitivity reactions to procarbazine with mechlorethamine, vincristine, and procarbazine chemotherapy in the treatment of glioma. *Cancer*. 1992; 69:2532–2540.
 68. Lehmann DF, Hurteau TE, Newman N, Coyle TE. Anticonvulsant usage

- is associated with an increased risk of procarbazine hypersensitivity reactions in patients with brain tumors. *Clin Pharmacol Ther.* 1997;62:225–229.
69. Brooks BJ, Hendler NB, Alvarez S, Ancalmo N, Grinton SF. Delayed life-threatening pneumonitis secondary to procarbazine. *Am J Clin Oncol.* 1990;13:244–246.
 70. Mahmood T, Mudad Raja. Pulmonary toxicity secondary to procarbazine. *Am J Clin Oncol.* 2002;25:187–188.
 71. O'Dwyer PJ, King SA, Fortner CL, Leyland-Jones B. Hypersensitivity reactions to teniposide (VM-26): an analysis. *J Clin Oncol.* 1986;4:1262–1269.
 72. Kellie SJ, Crist WM, Pui CH, et al. Hypersensitivity reactions to epipodophyllotoxins in children with acute lymphoblastic leukemia. *Cancer.* 1991;67:1070–1075.
 73. Zanotti KM, Markman M. Prevention and management of antineoplastic-induced hypersensitivity reactions. *Drug Safety.* 2001;24:767–779.
 74. Hoetelmans RMW, Schornagel JH, Bokkeel Huinink WW, Beijnen JH. Hypersensitivity reactions to etoposide. *Ann Pharmacother.* 1996;30:367–371.
 75. Hartmann JT, Lipp HP. Camptothecin and podophyllotoxin derivatives. *Drug Safety.* 2006;29:209–230.
 76. Nolte H, Carstensen H, Hertz H. VM-26 (teniposide)-induced hypersensitivity and degranulation of basophils in children. *Am J Pediatr Hematol Oncol.* 1988;10:308.
 77. Carstensen H, Nolte H, Hertz H, Jensen T. Hypersensitivity reactions to teniposide in children. *J Clin Oncol.* 1987;5:1491–1492.
 78. Hudson MM, Weinstein HJ, Donaldson SS, et al. Acute hypersensitivity reactions to etoposide in a VEPA regimen for Hodgkin's disease. *J Clin Oncol.* 1993;11:1080–1084.
 79. Siderov J, Prasad P, De Boer R, Desai J. Safe administration of etoposide phosphate after hypersensitivity reaction to intravenous etoposide. *Br J Cancer.* 2002;86:12–13.

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Objectives: After reading this article, participants should be able to demonstrate an increased understanding of their knowledge of allergy/asthma/immunology clinical treatment and how this new information can be applied to their own practices.

Participants: This program is designed for physicians who are involved in providing patient care and who wish to advance their current knowledge in the field of allergy/asthma/immunology.

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CME Examination

1–5, Lee C, Gianos M, Klaustermeyer WB. 2009;102:179–187.

CME Test Questions

1. Skin testing has been validated for which of the following chemotherapeutic agents?
 - a. paclitaxel
 - b. etoposide
 - c. asparaginase
 - d. carboplatin
 - e. procarbazine
2. Hypersensitivity reactions related to which of the following chemotherapy agents are thought to be non-IgE mediated, with most reactions occurring with the first or second dose?
 - a. teniposide
 - b. carboplatin
 - c. paclitaxel
 - d. procarbazine
 - e. cisplatin
3. Which of the following statements is FALSE?
 - a. Abraxane, a Cremophor EL-free albumin bound paclitaxel, is not associated with significant hypersensitivity reactions.
 - b. L-asparaginase is the chemotherapy agent with the highest frequency of hypersensitivity reactions.
 - c. Fluid retention related to docetaxel therapy may be delayed with corticosteroids.
 - d. Premedication with corticosteroids and antihistamines is not effective in the management of infusion reactions associated with paclitaxel.
 - e. Hypersensitivity reactions to procarbazine are difficult to predict.
4. A type III hypersensitivity reaction manifesting as pulmonary toxicity is associated with which agent?
 - a. procarbazine
 - b. L-asparaginase
 - c. cisplatin
 - d. teniposide
 - e. carboplatin
5. Options for a patient who has a hypersensitivity reaction to *Escherichia coli*-derived L-asparaginase include all of the following except:
 - a. substitute with *Erwinia*-derived L-asparaginase
 - b. desensitization
 - c. pegaspargase
 - d. discontinue reaction until reaction resolves then restart at slower rate
 - e. discontinue treatment with asparaginase

Answers found on page 222.