Hypersensitivity reactions to antineoplastic agents: an overview

Ekaterini Syrigou[a], Nektaria Makrilia[a], Ioanna Koti[a], Muhammad W. Saif[b] and Kostas N. Syrigos[a,b]

Hypersensitivity reactions to antineoplastic agents are defined as unexpected reactions with signs and symptoms inconsistent with known toxicity of antineoplastic drugs. These reactions are uncommon and usually associated with certain antineoplastic categories, such as taxanes, platinum-containing compounds, epipodofyllotoxins, asparaginase, procarbazine and, more rarely, with doxorubicin and 6-mercaptopurine. The mechanisms that are responsible for hypersensitivity reactions are unclear and vary between agents. Symptoms of these reactions range from mild skin rashes to more severe reactions, such as arthralgia, respiratory arrest or even death in some cases. Once hypersensitivity reactions are observed, basic principles that allow their management and possible continuance and completion of the regimen should be followed. ***Anti-Cancer Drugs*** **20:1–6 © 2009 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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[a]Oncology Unit, 3rd Department of Medicine, Athens School of Medicine, Sotiria General Hospital, Athens, Greece and [b]Department of Clinical Oncology, Yale School of Medicine and Cancer Center, Connecticut, USA

Correspondence to Kostas N. Syrigos, MD, PhD, Assistant Professor and Head, Oncology Unit, 3rd Department of Medicine, Athens School of Medicine, Building Z, Sotiria General Hospital, Mesogion 152, 115 27 Athens, Greece
Tel: +30 210 7475 034; fax: +30 210 7781 035;
e-mail: knsyrigos@usa.net; ksyrigos@med.uoa.gr

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Introduction

Hypersensitivity represents only a small proportion of adverse reactions of antineoplastic agents. Approximately 80% of adverse drug reactions are predictable and common [1]. Hypersensitivity reactions are unpredictable and not related to the pharmacologic reactions of the drug and are defined as unexpected reactions with signs and symptoms not consistent with known toxicity of the drug [2]. Hypersensitivity reactions are frequently associated with certain antineoplastic categories, such as taxanes, platinum-containing compounds, epipodophyllotoxins, asparaginase, procarbazine and, occasionally, doxorubicin and 6-mercaptopurine [3].

Pathogenetic mechanisms that are associated with the development of these reactions are unclear. Immunopathologic drug reactions are generally classified in four categories (Table 1). These drug reactions are sometimes difficult to clinically distinguish from pseudoallergic reactions. Symptoms vary from mild cutaneous eruptions to severe reactions such as respiratory arrest, cardiogenic shock or even death. Severe hypersensitivity reactions are, however, rare with an incidence of less than 5% [3].

Once hypersensitivity reactions occur, the issue of continuance and completion of therapy is raised. In the case of mild reactions, readmission by lowering the infusion rate and using premedication therapy could be considered. If equally effective non-cross-reacting alternative drugs are available, they should be used. Otherwise, desensitization is an option.

We will try to review the hypersensitivity reactions associated with each of the main antineoplastic agents used today.

L-asparaginase

L-asparaginase is an enzyme used in the treatment of acute lymphoblastic leukaemia.

Incidence

Incidence is high. It is estimated that hypersensitivity reactions occur in 6–43% of patients after intravenous infusion. For this reason, L-asparaginase is now mainly administered by the intramuscular or subcutaneous route [2]. Intramuscular infusion is, however, also associated with hypersensitivity reactions. It has been reported that allergic reactions occurred in 25% of patients treated with weekly high-dose intramuscular *Escherichia coli* asparaginase [4]. Risk factors for allergic reactions are intervals between therapy courses longer than 1 month, the administration of the drug at weekly intervals, as well as a history of previous exposure to L-asparaginase even if it had not caused any reaction then.

Clinical manifestations

Allergic reactions occur in the first hours after administration and are typical of IgE-mediated hypersensitivity

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Table 1 Pathogenetic mechanisms of hypersensitivity reactions to chemotherapeutic agents

Type I	IgE mediated	Acute anaphylaxis Urticaria
Type II	C-dependent cytolysis	Haemolytic anaemia Thrombocytopenia Interstitial nephritis
Type III	Immune complex damage	Serum sickness Drug fever Cutaneous eruptions and vasculitis
Type IV	Cellular hypersensitivity	Contact dermatitis Morbilliform eruptions

reactions. Symptoms include skin rash, respiratory distress and acute anaphylaxis [5].

Pathogenesis

Although the clinical features are typical, IgE mechanism has not been established. Researchers have found a statistically important higher rise of IgG-specific L-asparaginase antibodies in children who had experienced hypersensitivity reactions compared with those with no such reactions [6,7].

L-asparaginase is produced from *E. coli*. Granulocyte-colony stimulating factor is also derived from *E. coli*. Cross-reaction between them has been reported [8]. Alternatively, L-asparaginase could be produced from Erwinia and could be used in case of hypersensitivity reaction to the *E. coli* [4].

Management

An intradermal skin test should be performed before the initial administration of L-asparaginase as well as when it is given after an interval of a week or more between doses. The skin test site should be observed for at least 1 h for the appearance of a wheal or erythema. A negative skin test reaction does not preclude the possibility of development of an allergic reaction [8].

Patients who had experienced allergic reactions could be rechallenged with Erwinia-produced asparaginase. Another option is pegaspargase. Pegaspargase is a polyethylene glycol conjugated form of L-asparaginase. The majority of patients with hypersensitivity to L-asparaginase tolerate pegaspargase without further clinical hypersensitivity [9].

Desensitization protocols consist of progressively increasing doses of asparaginase while adequate precautions are taken to treat an acute allergic reaction. One reported schedule begins with a total of 1 IU given intravenously and doubles the dose every 10 min [8].

Epipodophyllotoxins

Epipodophyllotoxins include teniposide (VM26) and etoposide (VP16). Etoposide is used for several malignancies such as testicular, bladder, prostate, lung, stomach, uterine and brain cancer. Teniposide is used for acute lymphocytic leukaemia (particularly in children) and for neurological malignancies.

Incidence

Teniposide is related to higher incidence of hypersensitivity reactions comparing with etoposide [2]. According to a study, the incidence of hypersensitivity reactions to teniposide and etoposide in 108 children with acute lymphoblastic leukaemia was (46%) as 50 out of the 108 patients had one or more hypersensitivity reactions. The risk of any child having a reaction was 52% for teniposide, compared with 34% for etoposide [10].

Clinical manifestations

In most cases, symptoms occur during the first minutes of the first or second course but no IgE-mediated mechanism or histamine release have been established. Signs and symptoms include flushing, facial oedema, urticaria, respiratory problems, blood pressure fluctuations, tachycardia and abdominal pain. No fatal outcome has been reported [11]. In addition, both of these drugs induce hypotension in 1–2% of patients after rapid intravenous infusion. This infusion reaction could be prevented if drugs are infused slowly over a period of 30–60 min with close medical observation [2]. Each millilitre of teniposide solution contains 10 mg of drug and 500 mg of cremaphor EL, a polyoxyethylated castor oil solvent. This solvent is also added to paclitaxel and cyclosporin intravenous solutions and it has been reported to be related with hypersensitivity reactions [2].

Management

Once hypersensitivity reactions occur, infusion should be stopped and a rapid assessment and maintenance of airway, breathing and circulation must be performed. Premedication with steroids and antihistamines could be attempted. In studies rechallenging with slower infusion rate was successful in 78% of cases [12]. There is limited evidence to establish cross reactivity between teniposide and etoposide.

Taxanes

Paclitaxel is used for the treatment of breast, ovarian, lung, bladder, prostate, melanoma, oesophageal, as well as other types of solid tumour cancers. Docetaxel has been approved for the treatment of breast, non-small cell lung, advanced stomach, head and neck and metastatic prostate cancer.

Incidence

The incidence of hypersensitivity reactions associated with taxane regimen is 2–5% without premedication therapy and is reduced to 1–2% when premedication therapy (steroids and antihistamines) is administered.

Severe anaphylactic reactions may occur in 2–4% of patients treated with paclitaxel and 2% of patients treated with docetaxel [13]. Four risk factors have been identified, including history of mild dermal reactions in previous courses, respiratory dysfunction, obesity and the female patient being postmenopausal at the time of ovariectomy [14].

Table 2 Recommended premedication therapy for taxanes

20 mg dexamethasone orally, the night before and the morning of administration	20 mg dexamethasone 30 min before administration
50 mg diphenydramine 30 min before administration	50 mg diphenydramine 30 min before administration
20 mg famotidine intravenously, 30 min before administration	20 mg famotidine intravenously, 30 min before administration

Clinical features

Hypersensitivity reactions to taxanes occur mainly during the first or second infusion [2]. Their severity ranges from mild to severe and could even be life threatening. A case of a patient who experienced fatal hypersensitivity reaction after paclitaxel administration despite premedication therapy was reported [14]. Symptoms include skin rash, hypotension, dyspnoea and abdominal pain [2].

Pathogenesis

Although there are reports that suggest that previous allergy history increases the incidence of hypersensitivity reactions to taxanes, no IgE-mediated mechanism has been established. The allergic nature of hypersensitivity-type reactions to taxanes has been questioned. Plasma histamine and serum tryptase were measured in patients with hypersensitivity reactions after docetaxel therapy compared with a control group and they concluded that hypersensitivity reactions to docetaxel do not seem to be histamine or tryptase mediated. Component C is considered to play a vital role [14].

Both paclitaxel and docetaxel are highly hydrophobic compounds and require synthetic solvents for parenteral administration. These solvents could induce severe or even life-threatening side effects. Nanoparticle albumin-bound paclitaxel (nabP, arbaxane) is a novel, solvent-free formulation of paclitaxel and it has been suggested that nabP can be administered safely even without steroid and antihistamine premedication. In 2004, the US Food and Drug Administration approved the use of nabP for treatment of metastatic breast cancer after failure of an anthracycline-based regimen [15].

Management

Premedication therapy has been established to prevent severe hypersensitivity reactions to taxanes (Table 2). A common pretreatment therapy is 40 mg of dexamethasone or equivalent orally 12 and 6 h before paclitaxel administration plus diphenhydramine and histamine-2-receptor antagonist 30 min before the infusion [2]. Premedication therapy does not eliminate reactions but minimises the incidence and severity of symptoms. Intravenous prophylaxis regimen (diphenhydramine 50 mg, famotidine 20 mg, dexamethasone 20 mg) given 30 min before paclitaxel (without any earlier oral steroid doses), however, has been suggested as an alternative and more convenient regimen. The incidence of hypersensitivity reactions is comparable with that reported for the classic protocol.

A study reports 90% cross-sensitivity between docetaxel and paclitaxel [16]. Consequently, caution is required when rechallenging patients with docetaxel, if they have previously reacted to paclitaxel. Desensitization is another option when taxane therapy is effective.

Platine compounds

Carboplatin, cisplatin and oxaliplatin are antineoplastic drugs are classified as 'alkylating agents' used in the treatment of a variety of cancers such as testicular, ovarian, lung, breast, cervical, stomach and prostate cancer, colon or rectal cancer.

Incidence

Hypersensitivity reactions have been reported in 10–27% of patients treated with cisplatin or carboplatin [2]. Although hypersensitivity reactions may occur during first infusion, their incidence increases with multiple courses and are generally noticed after six to eight courses [3].

There seems to be a relationship between history of systemic allergic reactions and risk of subsequent carboplatin hypersensitivity. A retrospective analysis concluded that patients with a history of systemic hypersensitivity to medication or environmental exposure may be at a higher risk of allergic reactions to carboplatin [17]. The incidence of hypersensitivity reactions after oxaliplatin administration is comparable to that of the earlier generation platinum agents following the increasing use of oxaliplatin in clinical practice [18].

Clinical features

Hypersensitivity reactions to platine salts occur typically during the first few minutes of infusion. Clinical manifestations vary from mild, such as itching or erythema (mainly of the palms and soles) to more severe reactions, such as tachycardia, wheezing, facial swelling, throat and chest tightness, hypertension or hypotension or even respiratory arrest. Delayed hypersensitivity reactions have also been reported, such as three cases of severe immunologic thrombocytopenia (platelets $< 2000/mm^3$) [17].

Pathogenesis

The precise pathogenetic mechanism is currently unknown. The characteristic clinical manifestations suggest

a type I IgE-mediated reaction. These reactions must be distinguished from the idiosyncratic infusional reactions that are associated with a massive release of cytokines [18].

Skin tests

A review in the literature implies that skin tests may be useful for recognizing patients at high risk of developing hypersensitivity at platine salts. A negative carboplatin skin test seems to predict the absence of a severe hypersensitivity reaction with reasonable reliability, whereas the implications of a positive test remain less certain. In a monocentric prospective study patch tests, prick tests and intradermal tests with cisplatin, carboplatin and oxaliplatin were performed. Out of 21 patients that were enrolled, 14 had positive skin tests. Prick tests were positive in five cases, in which hypersensitivity reaction occurred within less than 2 h. Intradermal tests were positive in 12 of 19 patients with the suspected platine salts. All patients with early symptoms (< 2 h) had at least one positive skin test (prick tests and/or IDT). In contrast, all patients who had experienced delayed symptoms had negative skin tests [19].

Management

When hypersensitivity reactions to platine salts do occur, symptoms generally respond to discontinuation of treatment and administration of fluids, steroids and antihistamines, oxygen and possibly epinephrine (Table 3). Withdrawal of platine therapy is strongly suggested after sudden and severe thrombocytopenia. Patients with mild allergic reactions may be rechallenged to therapy by lowering the rhythm of infusion and by administering premedication with steroids and H1 and H2 inhibitors. According to the literature, however, premedication with steroids and antihistamines is not as effective in preventing hypersensitivity reactions to platinum-containing agents as it is for taxanes [2].

Several successful cases of cisplatin rechallenge after carboplatin hypersensitivity have been reported, but this is suggested only after careful consideration of potential risks and benefits and always under close monitoring of the patient. Desensitization protocols have been suggested for the readministration of platine salt therapy after hypersensitivity reactions [20]. Results are promising [21–24] (Table 4).

Table 3 General measures for the management of anaphylactic reactions during an antineoplastic regimen

1. Discontinuation of infusion
2. Recumbent position of patient
3. High-flow oxygen administration
4. Fluid resuscitation
5. Epinephrine administration
6. H_1 and H_2 antihistamines
7. Corticosteroids
8. Vasopressors
9. Glucagon for persistent hypotension in patients taking β-blockers

Table 4 Reported desensitization protocols for oxaliplatin

Reference	Premedication	Initial dose	No. of doses	Total time	Cycles completed
[21]	No	1/10 000	12	3.5 h	13
[22]	Yes	1/10 000	Not reported	8 h	5
[23]	Yes	1/10 000	5	6 h	6
[24]	No		Continual	24 h	2

Anthracyclines

Anthracyclines (doxorubicin, daunorubicin, idarubicin and epirubicin) are used for the treatment of various cancers such as bladder, breast, prostate, sarcomas, lung cancer as well as leukaemia, lymphomas, multiple myeloma and neuroblastoma. Anthracycline therapy is occasionally accompanied by hypersensitivity reactions [2]. Pegylated liposomal doxorubicin has been reported to cause immediate hypersensitivity reactions in 9% of patients. It is, however, reported to cause less alopecia, cardiotoxicity, nausea and vomiting compared with free doxorubicin [25]. These reactions occur mainly in the first minutes of administration and symptoms include skin flares, urticaria, and rarely angioneurotic oedema, dyspnoea or anaphylaxis. Component C activation is believed to be the pathogenetic mechanism [26].

Of the first 35 patients in a phase II study of pegylated-liposomal doxorubicin, three developed dyspnoea, two developed low back pains and two patients developed pain at the site of tumour, within 1–5 min after starting the infusion. The symptoms resolved within 5–15 min after stopping the infusion [27]. No evidence is available that premeditation therapy with steroids and antihistamines could prevent these reactions.

Procarbazine and dacarbazine

Procarbazine is an alkylating agent that is used in the treatment of brain tumours, advanced Hodgkin's disease and bronchogenic carcinoma.

Hypersensitivity reactions are common in patients treated with this procarbazine. Brain tumours are related with higher incidence of hypersensitivity reactions compared with other malignancies [2]. It has also been reported that anticonvulsant therapy increases the risk of allergic reactions. Clinical features of hypersensitivity reactions are maculopapular rash, fever, reversible abnormal liver function test results and pulmonary toxic effects [28]. No case of successful rechallenge of the drug in patients with severe hypersensitivity reactions has been reported in the literature.

Dacarbazine is used for treatment of metastatic malignant melanoma, Hodgkin's disease, soft tissue sarcomas,

neuroblastoma, and rhabdomyosarcoma and medullary carcinoma of the thyroid. Hypersensitivity associated with this intravenous agent is rare and includes erythemateus and urticarial rashes, fever, chills, malaise and myalgias [2].

Chlorambucil and melphalan

Chlorambucil and melphalan are alkylating agents used in the treatment of bladder cancer. Allergic reactions to chlorambucil are rare. Acute onset of high fever and progressive immune haemolytic anaemia have been reported after chlorambucil administration [29]. Two cases with identical symptoms of lymphadenopathy have been reported. When patients were rechallenged with chlorambucil, identical reactions occurred. No cross-reactivity between chlorambucil and other alkylating agents have been described in literature. Hypersensitivity reactions to melphalan occur more often when it is given intravenously. Symptoms include urticaria, angioedema and toxic epidermal necrolysis [30].

Cyclophosphamide and ifosfamide

Cyclophosphamide is used in the treatment of various malignancies such as lymphoma and leukaemia, gynaecological, brain and lung cancer. It is also widely used in the treatment of vasculitis and systemic lupus erythematosus. Ifosfamide is also used in treatment of head and neck cancer.

Cyclophosphamide can cause hypersensitivity reactions when given intravasculary as well as orally, although reactions are rare in oral administration. Clinical manifestations vary from skin rash to respiratory distress and vasculitis. Reactions occur typically several hours after administration (delayed type of hypersensitivity) and there is evidence that IgE immediate type of mechanism is involved. Skin tests with cyclophosphamide and its metabolites have been developed to recognize the potential risk of hypersensitivity reactions. In a skin test protocol patients with late-onset allergic reactions had positive immediate skin test results to cyclophosphamide metabolites but not to cyclphosphamide itself [31]. This report is an indication of the role of cyclophosphamide metabolites in pathogenesis of allergic reactions. Hypersensitivity reactions to ifosfamide occur in less than 1% of patients [2]. No enough evidence exists in the literature.

Cytarabine and fludarabine

Cytarabine and fludarabine are antimetabolites that are used to treat different forms of leukaemia and non-Hodgkin's lymphoma. Hypersensitivity reactions associated with these antimetabolites are rare but they can be severe or even result in anaphylactic shock. Although there is not enough evidence in the literature, an IgE-mediated mechanism has been suggested. When continuance of therapy is essential, desensitization is a potential option.

Bleomycin

Bleomycin is used for the treatment of squamous cell cancer, melanoma, sarcoma and lymphoma. Bleomycin causes hypersensitivity reactions in 1% of patients with lymphoma and less than 0.5% of those with solid tumours. The symptoms are fever, hypotension and, in few cases, cardiovascular collapse. The pathogenetic mechanism is unknown. Discontinuance of infusion and administration of fluids, steroids, antihistamines and antipyretics should be immediate once symptoms occur [32].

Plant alkaloids

Vinorelbine is a plant alkaloid used in the treatment of non-small cell lung cancer and breast cancer. No reports are available in the literature about hypersensitivity reactions after vinorelbine administration. Allergic reactions to vinblastine are rare. Vincristine is used for the treatment of bladder cancer, Wilm's tumour and Kaposi's sarcoma. It was reported that a patient with acute leukaemia developed anaphylactoid reaction and pulmonary haemorrhage but normal serum tryptase levels suggested that it was secondary to tumour lysis, rather than to a mast cell-mediated anaphylactic reaction to vincristine [33].

Mercaptopurine

Mercaptopurine is used in leukaemia and inflammatory bowel disease. Allergic reactions are rare. In a single institute study, 2.7% of patients suffered hypersensitivity reactions, with fever being the most common. Nine of these patients were rechallenged with 6-MP with recurrence of the same symptoms. It has been suggested that thioguanine (6-TG), a closely related thiopurine, could be an alternative solution in patients that have experienced hypersensitivity reactions from mercaptopurine or azathioprine [34].

Fluorouracil

5-Fluorouracil is an antimetabolite used in the treatment of colorectal, breast and other types of cancer. There is not enough evidence concerning hypersensitivity reactions after therapy with 5-fluorouracil [2].

Monoclonal antibodies

Monoclonal antibodies (cetuximab, rituximab, trastuzumab, gemtuzumab ozogamicin, alemtuzumab, ibritumomab tiuxetan) are new antineoplastic agents that target specific malignant cell receptors. In addition, antibodies can carry substances to the targeted cells, such as radioactive isotopes, toxins and antineoplastic agents.

Incidence

High incidence of hypersensitivity reactions has been observed. The incidence is 40% for trastuzumab, 77% for rituximab, 19% for cetuximab and 5% for the fully human panitumumab [2,3].

Clinical manifestations

Symptoms occur mainly during the first or the second administration. Symptoms vary from mild and moderate, such as rash, to severe, such as bronhospasm, chest pain and anaphylaxis.

Pathogenesis

Pathogenesis is not clear. Although symptoms resemble type I reactions, their main occurrence during first infusion demonstrates that no sensitization is necessary. It has been suggested that acute reaction after monoclonal antibodies administration is induced by cytokine release.

Management

When hypersensitivity reactions occur, infusion should be stopped. Readministration at a lower rate is an option after mild-to-moderate reactions. Hypersensitivity reactions could also been prevented with premedication therapy. Continuance of the regimen with an equally effective different agent is also possible [3].

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