

Evaluation and management of hypersensitivity reactions to chemotherapy agents

Elizabeth Huiwen Tham,^{1,2} Yew Kuang Cheng,³ Miah Hiang Tay,⁴
 Ana Patricia Alcasabas,^{1,2} Lynette Pei-Chi Shek^{1,2}

¹University Children's Medical Institute, National University Hospital, Singapore, Singapore

²Department of Paediatrics, Yong Loo Lin School of Medicine, National University of Singapore, Singapore, Singapore

³Department of Allergy, Arthritis & Rheumatism Clinic, Gleneagles Medical Centre, Singapore, Singapore

⁴Oncocare Clinic, Gleneagles Medical Centre, Singapore, Singapore

Correspondence to

Lynette Pei-Chi Shek, Division of Allergy & Immunology, Department of Paediatrics, Khoo Teck Puat-National University Children's Medical Institute (KTP-NUCMI), 1E Kent Ridge Road, NUHS Tower Block Level 12, Singapore 119228, Singapore; lynette_shek@nuhs.edu.sg

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ABSTRACT

Hypersensitivity reactions to chemotherapy drugs pose significant difficulties in management, especially when no suitable alternative is available or acceptable and delay in continuation of treatment may be life-threatening. Such reactions may be IgE- or non-IgE-mediated and have varied manifestations. Timely recognition and treatment of life-threatening hypersensitivity reactions are essential. Identification of patients at high risk of developing hypersensitivity reactions allows risk stratification to guide clinical decision-making. Skin testing for carboplatin hypersensitivity has good predictive value but is not yet established for oxaliplatin and taxane hypersensitivity. Rapid desensitisation may be considered if no suitable alternative drug is available. Available protocols have shown good safety and efficacy but must be performed in an appropriate setting with adequate monitoring. There are many avenues for research into the utility of skin testing for other chemotherapy agents as well as in vitro tests.

INTRODUCTION

Advances in cancer research and the development of increasingly sophisticated treatment regimens have led to a corresponding increase in exposure to chemotherapeutic agents. Hypersensitivity reactions have been documented with use of many antineoplastic drugs such as asparaginase, anthracyclines, 6-mercaptopurine, epipodophyllotoxins, platins and taxanes. Previously, the development of significant hypersensitivity reactions precluded continued administration of the inciting drug, with the potential withholding of first-line, life-saving chemotherapy from affected patients.

There has been a recent, growing interest in understanding these hypersensitivity reactions and their management. Platins and taxanes form the cornerstone of many oncology protocols and are essential for effective treatment of many cancers, thus continuation of therapy in the face of hypersensitivity reactions is a challenge that must, and can, be surmounted rather than avoided. In many centres, the use of premedications and development of desensitisation regimens have successfully overcome these barriers to therapy, allowing patients to continue receiving optimal oncological care rather than medical therapy being restricted to less efficacious second-line agents.

Platins and taxanes are the most common chemotherapy agents used in modern oncology regimens and are also associated with the highest rates of hypersensitivity reactions. Extensive experience in management of these reactions has been

reported in the literature, and several successful desensitisation protocols are available. In contrast, literature on other chemotherapy agents is limited and evidence likewise less robust, and hence these will not be discussed here.

CHEMOTHERAPEUTIC AGENTS

Platinum agents

Platins are the first line of therapy for solid organ malignancies such as ovarian cancer. Cisplatin, the first commercially developed drug in this class, is unfortunately also associated with significant neurotoxicity, nephrotoxicity and myelosuppression. Carboplatin was thus subsequently developed for its relatively less toxic side effects. The newest generation of platinum drugs is oxaliplatin, which is first-line therapy for metastatic colorectal carcinoma and is also used in various other malignancies such as breast carcinoma, non-Hodgkin's lymphoma, non-small-cell lung carcinoma and ovarian carcinoma.

Taxanes

Docetaxel is a semisynthetic taxane derived from 10-deacetylbaccatin III found in *Taxus baccata*,¹ a European Yew tree. It acts as an antitubulin agent and is primarily used for treatment of breast, ovarian, prostate and non-small-cell lung cancer. In paediatric cancers, it is a salvage regimen for relapsed or refractory sarcomas. Paclitaxel, derived from the Pacific Yew tree, *Taxus brevifolia*, is commonly used in the treatment of breast, ovarian, lung and pancreatic cancer.

EPIDEMIOLOGY OF HYPERSENSITIVITY REACTIONS

Platins and taxanes are used in many modern chemotherapy protocols and also form the largest group of chemotherapeutic agents implicated in hypersensitivity reactions. The incidence of platin hypersensitivity increases with exposure. Rates of reactions to carboplatin have been shown to increase from less than 1% in five or fewer chemotherapy cycles to 19.5% after eight cycles.² Reactions to cisplatin have been described in only about 5%,³ whereas the incidence in patients receiving oxaliplatin is around 13%, of which only 0.5% are severe.⁴

Hypersensitivity reactions to taxanes, conversely, were found to be as high as 30% of patients in initial phase II trials⁵; however, the incidence has since declined to around 3–5% with the widespread use of premedications.^{6,7}

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MECHANISMS OF HYPERSENSITIVITY AND CLINICAL MANIFESTATIONS

Platins

Hypersensitivity reactions to platinum drugs are mainly of the immediate, IgE-mediated type. Early observations in support of this mechanism include the typical 'sensitisation' period characterised by several uncomplicated exposures, typically up to seven cycles,⁸ preceding the eventual reaction,³ onset of reaction within the first 60 min of administration, and the classical symptomatology. Type I IgE-mediated hypersensitivity reactions are characterised by the development of cutaneous symptoms (such as flushing, urticaria and angioedema), cardiorespiratory compromise (such as hypotension, wheezing and throat tightness) and abdominal symptoms (such as nausea, vomiting, abdominal cramps and diarrhoea), typically within the first hour of exposure to the inciting drug.

In vitro studies have shown that type I hypersensitivity to platins involves cross-linking of specific IgE bound to FcεRI IgE receptors on the surface of mast cells and basophils. This results in the release of vasoactive inflammatory mediators including histamine, tryptase, prostaglandins and leukotrienes, propagating the inflammatory cascade, which culminates in the clinical manifestations of hypersensitivity.⁹ Skin tests are also positive in more than 80% of these patients, consistent with an IgE-mediated process.¹⁰

Interestingly, oxaliplatin has also been reported to be associated with type II hypersensitivity reactions, such as drug-induced thrombocytopenia and haemolytic anaemia,^{11 12} as well as delayed-type reactions.¹³

Taxanes

The mechanism of hypersensitivity to taxanes, however, is less well defined. It was previously thought that all reactions were of the non-immediate, non-IgE-mediated type. Proposed mechanisms include direct mast cell activation,¹⁴ complement activation resulting in immune complex formation,¹⁰ and release of nitric oxide and cytokines leading to kinin formation.¹⁵ Unlike platins, reactions to taxanes, while manifesting similarly with urticaria, bronchospasm and hypotension, may occur during the first exposure without apparent prior sensitisation, thus supporting the non-IgE-mediated theory.^{14 16} Type II complement-mediated reactions resulting in thrombocytopenia, haemolysis and Evans syndrome, as well as type III antigen-antibody complex formation (urticarial vasculitis), have also been reported.¹⁷

It has been suggested that Cremophor, the castor-oil-based excipient for paclitaxel, is responsible for activation of the complement pathway culminating in observed hypersensitivity reactions.^{18 19} However, docetaxel, which does not contain Cremophor, has been implicated in similar reactions, pointing to the taxane moiety itself as the more likely culprit.⁸

There is now a growing body of evidence pointing to the possibility that some hypersensitivity reactions to taxanes may in fact be IgE-mediated. Prieto Garcia and Pineda de la Losa²⁰ found both in vivo and in vitro evidence of IgE positivity in a patient who suffered anaphylaxis on a second exposure to paclitaxel—with positive intradermal testing at a concentration of 0.1 µg/mL (0.0001 mg/mL) as well as a positive IgE dot-blot assay. Madrigal-Burgaleta *et al*²¹ and Gastaminza *et al*²² also described their experiences with patients with hypersensitivity reactions to paclitaxel and docetaxel, who had positive skin tests corroborated by appropriate controls, further strengthening the IgE hypothesis.

RISK FACTORS

Identification of risk factors associated with hypersensitivity reactions allows risk stratification to guide clinical decision-making for high-risk patients. A greater number of chemotherapy cycles, specifically more than eight,^{2 23} and a longer interval between cycles (47% if more than 24 months and 6.5% if less than 12 months)²⁴ have been shown to be associated with a higher risk of developing carboplatin hypersensitivity.

Risk factors for taxane hypersensitivity include an atopic history,²⁵ history of mild dermal reactions such as facial flushing and urticaria in previous courses, presence of respiratory dysfunction, obesity with a body mass index >25, and postmenopausal status.²⁶

DIAGNOSTIC TESTING

Skin testing protocols for carboplatin have been reported by several centres and are available in the literature.²⁷ In one study, skin testing to carboplatin was found to have a 98–99% negative predictive value,²⁸ whereas a positive skin test was strongly indicative of a likelihood of reaction with continued administration. Markman *et al*²⁹ found that six out of seven patients (86%) with positive skin tests subsequently developed symptoms of anaphylaxis on retreatment.

This has, however, not held true for oxaliplatin hypersensitivity reactions, for which studies on skin prick and intradermal testing, mostly with small numbers, have shown conflicting results lacking statistical significance,^{11 30–32} and no large-scale validation studies have yet been performed. Negative skin tests, however, do not exclude an IgE-mediated mechanism.

Routine skin testing has not been recommended for taxane hypersensitivity. Experience is generally limited,²² and some studies²¹ have demonstrated poor predictive values for skin prick and intradermal tests for docetaxel and paclitaxel. No established protocols are currently available, but, with mounting evidence for the role of type I hypersensitivity, pre-emptive skin testing, albeit still unvalidated in large trials, may eventually find its way into guidelines as a means of risk stratification for rechallenge or desensitisation of high-risk patients.

Caiado *et al*³³ described their experience with specific IgE testing for platin hypersensitivity. Carboplatin-specific IgE testing had a high specificity (100%) and excellent positive predictive value (100%) but low sensitivity (58.3%) and negative predictive value (50%). For oxaliplatin, it had higher sensitivity (75%) and negative predictive value (75%) but was less specific (75%) and had a lower positive predictive value (75%). However, in vitro testing has not been validated in large-scale studies and cannot yet be recommended for routine practice.

Skin testing should be performed only 4–6 weeks after a hypersensitivity reaction, as false negative results are common during that refractory period of mast cell hyporeactivity.^{34 35} Skin testing should only be performed by specialist allergists who are experienced in interpretation as well as management of rare, but possible, side effects such as anaphylaxis.

MANAGEMENT

Acute management

Timely recognition and management of acute hypersensitivity reactions are essential, and all staff involved in patient care should be well trained in this. In severe anaphylaxis, intramuscular epinephrine is life-saving, together with fluid resuscitation, supplemental oxygen, antihistamines, corticosteroids and bronchodilators.^{36 37}

Various options may then be considered for the remaining treatment regimen. In mild reactions, primary physicians may choose to continue with the infusion, even on the same day after symptoms have resolved with treatment,³⁸ occasionally with mild modifications such as halving the infusion rate.³⁹ Markman *et al*⁴⁰ successfully reinitiated paclitaxel infusions in 65 out of 70 patients (93%) as soon as 30 min after the development of hypersensitivity reactions, hypothesising that cytokine mediator depletion during the acute reaction results in subsequent hyporeactivity despite continued exposure to the inciting agent. For patients with more severe reactions, or in whom risk factors as detailed above can be identified, further precautionary steps may be necessary before continuation of therapy.

Risk stratification by skin testing

Some have recommended that skin testing be routinely performed for patients after the sixth course of carboplatin to identify patients at risk of a reaction with subsequent cycles.^{25 29} Zanotti *et al*²⁸ and Markman *et al*²⁹ showed that carboplatin skin testing had a 99% negative predictive value and was useful for predicting hypersensitivity reactions in subsequent exposures. Physicians caring for patients with positive skin tests to platins may thus consider alternative treatment regimens or, if no suitable alternatives are available, desensitisation. The recommendation cannot, however, be extrapolated to taxanes, as skin testing has yet to be validated as a prediction tool.

Premedications

Premedication involves administration of antihistamines and corticosteroids before infusion of the high-risk drug, to ameliorate

or attenuate any reactions that may occur. Premedication regimens with antihistamines and corticosteroids have not been reliably shown to be useful for hypersensitivity reactions to platins and thus cannot be routinely recommended.^{41 42} Attempts at pretreatment in patients with a history of previous reactions to platins have often resulted in hypersensitivity reactions of equal or even increased severity.⁴³

Several large centres have reported successful experiences with the use of premedication for desensitisation regimens involving paclitaxel and docetaxel, reducing the risk of hypersensitivity reactions from 30% to 3%^{14 44–46} (table 1), leading to widespread acceptance. For paclitaxel, either a two-step oral dexamethasone course (20 mg, 6 and 12 h before paclitaxel infusion) or a single intravenous dose 30 min before infusion were shown to be equally efficacious in a randomised controlled trial.⁴⁷

Docetaxel's premedication regimen requires either a single dose of intravenous dexamethasone 20 mg given 30 min before docetaxel infusion⁴⁸ or oral dexamethasone 16 mg/day (8 mg twice daily) for 3 days, starting 1 day before the start of chemotherapy. The latter regimen was shown to reduce the incidence of severe hypersensitivity reactions to docetaxel to only 2%.⁴⁹

For all the above regimens, the addition of H1 (intravenous diphenhydramine 50 mg) and H2 (intravenous ranitidine 50 mg) blockers is also essential.

Switching to a different drug in the same class

Cross-reactivity between carboplatin and cisplatin has been reported^{33 50} and can be attributed to similarities in their molecular structures. Thus patients who react to either drug are

Table 1 Hypersensitivity reactions to platins and taxanes and their management

Drug	Incidence	Reaction type and onset	Risk factors	Premedications	Skin testing	Desensitisation protocols
Carboplatin	<1–19.5%	IgE (type I)-mediated ► Flushing, urticaria, angioedema ► Hypotension ► Wheezing ► Nausea, vomiting, diarrhoea	1. Greater number of cycles (>8) 2. Longer interval between cycles	Not routinely recommended	SPT: 10 mg/mL ²⁷ IDT: 0.02 mL 3 steps 1. 1 mg/mL 2. 1 mg/mL 3. 3 or 5 mg/mL	5-step RUSH protocol ²⁷ 12-step standard protocol ²²
Cisplatin	~5%	Onset after several cycles	Not known			
Oxaliplatin	13%	IgE (type I)-mediated Type II or delayed-type reactions also ► Thrombocytopenia ► Haemolytic anaemia Onset after several cycles	Not known		Not validated	8-step rapid protocol ⁵³ Or 13-step high-risk protocol
Paclitaxel	3–5%	IgE (type I)- or non-IgE-mediated ► Flushing, urticaria, angioedema ► Hypotension ► Wheezing ► Nausea, vomiting, diarrhoea Type II ► Thrombocytopenia, haemolytic anaemia, Evans syndrome Type III ► Urticarial vasculitis Onset at 1st or 2nd cycle	1. Atopic history 2. Mild dermal reactions in previous courses 3. Respiratory dysfunction 4. Obesity 5. Postmenopausal ²⁶	1. PO dexamethasone 20 mg (6 and 12 h before) Or 2. IV dexamethasone 20 mg (30 min before)+IV diphenhydramine 50 mg+IV ranitidine 50 mg (30 min before) 1. PO Dexamethasone 8 mg BD (3 days, starting 1 day before) OR 2. IV dexamethasone 10 mg (30 min before)+IV diphenhydramine 50 mg+IV ranitidine 50 mg (30 min before)	Anecdotal, not validated	4-step protocol ^{25 55} 12-step standard protocol ^{8 22} 12-step standard protocol ^{8 54}
Docetaxel						

BD, twice a day; IV, intravenous; PO, by mouth.

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also likely to react if exposed to the second drug, thus switching between carboplatin and cisplatin is not recommended.

Patients who were sensitised to oxaliplatin were also found to be sensitised to carboplatin, but the converse did not hold true.³³ This is because oxaliplatin hypersensitivity is mediated by specific IgE antibodies against the platinum core, which is shared by all platinum salts. In carboplatin and cisplatin, however, IgE antibodies are directed against the primary amine groups, which are not present in oxaliplatin's molecular structure. However, larger clinical trials are needed before definite recommendations are made.

Desensitisation

If all the above measures are unsuccessful or if skin testing was negative but clinical suspicion is high, yet no suitable alternative chemotherapy regimens are available, desensitisation may be offered. Rapid desensitisation involves administration of incremental doses of drug in succession over a short period of time, allowing induction of temporary tolerance to drug antigens, eventually achieving full therapeutic doses that enable the patient to continue with optimal chemotherapy regimens.

Rapid desensitisation allows temporary, but not long-term, tolerance. Thus patients need to be redesensitised at each exposure. It has been hypothesised that the molecular basis for desensitisation for IgE-mediated reactions, through incremental exposure to the allergen, causes internalisation of FcεRI receptors and depletes signal transduction agents such as tyrosine kinases Lyn, Fyn and Syk. This renders mast cells unresponsive to further antigenic stimulation.^{51 52} The mechanisms in

non-IgE-mediated reactions remain unknown, but protocols founded on similar principles have been widely successful.

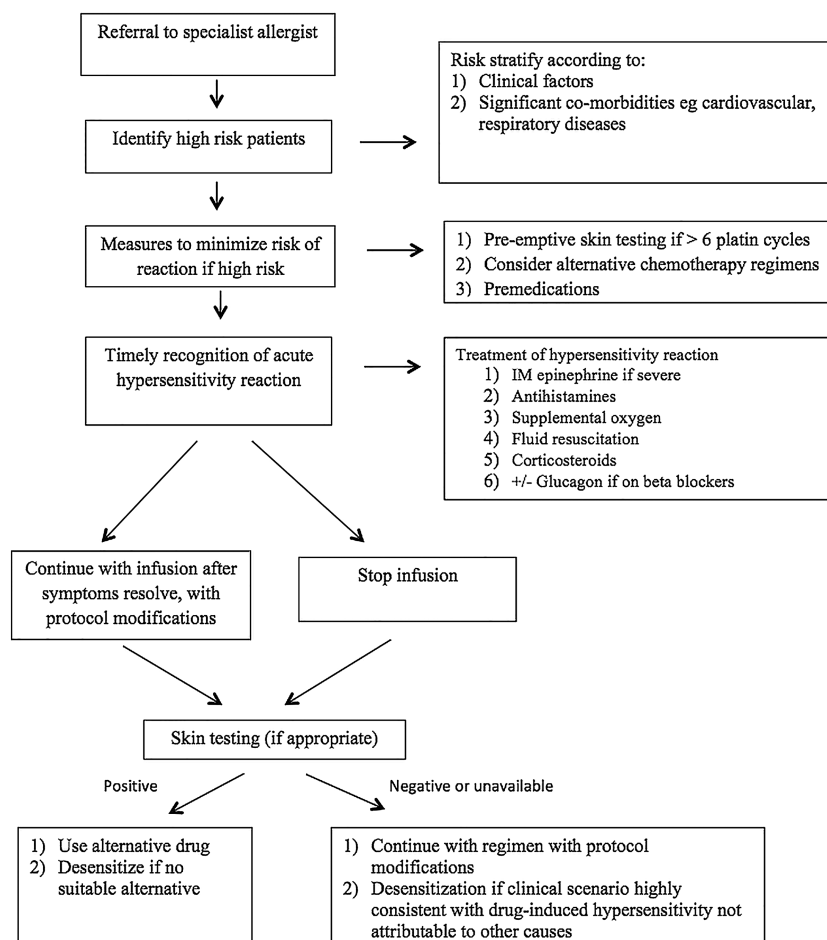
Various desensitisation protocols have been developed over the years for use in patients with gynaecological,^{22 35 38 53 54} breast,²² lung⁴⁹ and gastrointestinal^{11 55} malignancies. Routine preparation before any desensitisation procedure includes withholding beta blockers and ACE inhibitors for 24 h before the procedure.^{56 57}

Desensitisation is a high-risk procedure with risks of anaphylaxis and thus must only be carried out by trained allergists who are experienced in the diagnosis, evaluation and management of desensitisation and anaphylaxis. All desensitisation procedures should be carried out in a hospital setting—in the intensive care unit for the first desensitisation if the initial reaction was very severe, or if available and in milder reactions, an outpatient facility on the hospital grounds with continuous close monitoring and resuscitation facilities.³⁸ Premedication for desensitisation is similar to a regular infusion. H1 and H2 blockers should be routinely used even if not part of the original premedication regimen. Aspirin and montelukast may also be considered.⁵⁸

If hypersensitivity reactions occur during desensitisation, the infusion is stopped and treatment administered. Once symptoms resolve, the desensitisation may be allowed to continue and protocol amendments made for subsequent desensitisations. These may include the addition of a step, prolonging the duration of a step, or adding premedication before the step where the reaction previously occurred.³⁵

Established desensitisation protocols exhibit low rates of only mild hypersensitivity reactions (27% of 413 desensitisations in

Figure 1 Management algorithm for hypersensitivity reactions to chemotherapy agents. IM, intramuscular.



98 patients by Castells *et al*³⁵), with all patients successfully reaching full target doses of the implicated drug. Lee *et al*³⁸ showed that oncological outcomes were comparable to those for patients who had received the usual chemotherapy regimen as per institution guidelines. Goldberg *et al*⁵² and Lee *et al*⁵³ also demonstrated abolition of skin test positivity after desensitisation to carboplatin.

Desensitisation should not be offered for severe non-immediate hypersensitivity reactions, such as Stevens–Johnson syndrome and toxic epidermal necrolysis,⁵⁹ or type III hypersensitivity reactions, such as haemolytic anaemia or nephritis.⁶⁰

CONCLUSIONS

Hypersensitivity reactions to chemotherapy agents are increasing as cumulative exposure increases. Table 1 summarises these clinical characteristics and their management. Risk stratification based on known clinical factors, skin testing where appropriate, and individual institutions' experience in desensitisation procedures will be able to guide decision-making for high-risk patients.

The following stepwise treatment guideline is recommended (figure 1): (1) pre-emptive identification of high-risk patients and taking steps to minimise the likelihood of developing a reaction (skin testing for platin exposures after six cycles); (2) timely identification and treatment of an acute hypersensitivity reaction and using clinical judgement to guide continuation of the infusion if the reaction is mild; (3) skin testing where appropriate with controls; (4) desensitisation if there are no contraindications, but only by trained allergists experienced in this procedure, in a tertiary setting with adequate monitoring and resuscitation facilities.

More research is needed to elucidate the molecular mechanisms behind non-IgE-mediated hypersensitivity reactions and the role of desensitisation in abolishing these mechanisms. For IgE-mediated reactions, large-scale studies are needed to establish standardised protocols for skin testing and to evaluate the role of in vitro testing (specific IgE) in predicting the outcomes of subsequent exposures.

Multiple choice questions

Please answer true or false to be below,

- What type of hypersensitivity reactions have been reported for the following chemotherapy agents?
 - Carboplatin—Type II Evans syndrome
 - Oxaliplatin—Type II
 - Paclitaxel—Type IV Urticarial vasculitis
 - Docetaxel—Non-IgE-mediated reactions
- Skin testing for diagnosis of sensitisation has been established for docetaxel hypersensitivity
- Premedications have been shown to decrease the rates of hypersensitivity reactions in paclitaxel and docetaxel and are routinely recommended
- Desensitisation may be carried out for all of the following reactions
 - Generalised urticaria
 - Bronchospasm
 - Stevens–Johnson syndrome
 - Anaphylaxis

Main messages

- Hypersensitivity reactions to chemotherapy agents must be carefully evaluated with a risk-stratification protocol using a combination of patient clinical factors and skin testing, where relevant, to help to guide clinical decision-making for future treatment options.
- Possible management options after risk stratification, in the hands of experienced allergists only, may include judicious rechallenge with protocol modifications, switching to alternative drugs, premedication or desensitisation.
- Desensitisation protocols are available for most common chemotherapy agents and have shown good safety and efficacy, but should only be performed by trained allergists in a tertiary setting with resuscitation facilities.

Current research questions

- Validation of diagnostic skin test protocols for all chemotherapy agents.
- Validation of in vitro testing with specific IgE detection against chemotherapy agents.
- Mechanistic studies into the molecular basis for non-IgE-mediated hypersensitivity reactions—for example, for taxanes.

Key references

- Weiss RB, Donehower RC, Wiernik PH, *et al*. Hypersensitivity reactions from taxol. *J Clin Oncol* 1990;8:1263–8.
- Madrigal-Burgaleta R, Berges-Gimeno MP, Angel-Pereira D, *et al*. Hypersensitivity and desensitisation to antineoplastic agents: outcomes of 189 procedures with a new short protocol and novel diagnostic tools assessment. *Allergy* 2013;68:853–61.
- Gastaminza G, de la Borbolla JM, Goikoetxea MJ, *et al*. A new rapid desensitisation protocol for chemotherapy agents. *J Investig Allergol Clin Immunol* 2011;21:108–12.
- Shepherd GM. Hypersensitivity reactions to chemotherapeutic drugs. *Clin Rev Allergy Immunol* 2003;24:253–62.
- Castells MC, Tennant NM, Sloane DE, *et al*. Hypersensitivity reactions to chemotherapy: outcomes and safety of rapid desensitisation in 413 cases. *J Allergy Clin Immunol* 2008;122:574–80.

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REFERENCES

- Alsamarai S, Charpidou AG, Matthay RA, *et al*. Pneumonitis related to docetaxel: case report and review of the literature. *In Vivo* 2009;23:635–7.
- Sliesoraitis S, Chikhale PJ. Carboplatin hypersensitivity. *Int J Gynecol Cancer* 2005;15:13–18.
- Basu R, Rajkumar A, Datta NR. Anaphylaxis to cisplatin following nine previous uncomplicated cycles. *Int J Clin Oncol* 2002;7:365–7.

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- 4 Bautista MA, Stevens WT, Chen CS, *et al.* Hypersensitivity reaction and acute immune-mediated thrombocytopenia from oxaliplatin: two case reports and a review of the literature. *J Hematol Oncol* 2010;3:12.
- 5 Mertens WC, Eisenhauer EA, Jolivet J, *et al.* Docetaxel in advanced renal carcinoma. A phase II trial of the National Cancer Institute of Canada Clinical Trials Group. *Ann Oncol* 1994;5:185–7.
- 6 Rowinsky EK, Donehower RC. Paclitaxel (taxol). *N Engl J Med* 1995;332:1004–14.
- 7 Schrijvers D, Wanders J, Dirix L, *et al.* Coping with toxicities of docetaxel (Taxotere). *Ann Oncol* 1993;4:610–11.
- 8 Feldweg AM, Lee CW, Matulonis UA, *et al.* Rapid desensitization for hypersensitivity reactions to paclitaxel and docetaxel: a new standard protocol used in 77 successful treatments. *Gynecol Oncol* 2005;96:824–9.
- 9 Castells M. Update on mast cells and mast cell precursors and hypersensitivity responses. *Allergy Asthma Proc* 1997;18:287–92.
- 10 Szebeni J, Alving CR, Savay S, *et al.* Formation of complement-activating particles in aqueous solutions of Taxol: possible role in hypersensitivity reactions. *Int Immunopharmacol* 2001;1:721–35.
- 11 Wong JT, Ling M, Patil S, *et al.* Oxaliplatin hypersensitivity: evaluation, implications of skin testing, and desensitization. *J Allergy Clin Immunol Pract* 2014;2:40–5.
- 12 Garufi C, Vaglio S, Brienza S, *et al.* Immuno-hemolytic anemia following oxaliplatin administration. *Ann Oncol* 2000;11:497.
- 13 de Vries RS, Mattijssen EJ, van Sorge AA. Serious delayed hypersensitivity reaction to oxaliplatin. *Ann Oncol* 2006;17:1723–4.
- 14 Weiss RB, Donehower RC, Wiernik PH, *et al.* Hypersensitivity reactions from taxol. *J Clin Oncol* 1990;8:1263–8.
- 15 Mullins DW, Burger CJ, Elgert KD. Paclitaxel enhances macrophage IL-12 production in tumor-bearing hosts through nitric oxide. *J Immunol* 1999;162:8.
- 16 Peereboom DM, Donehower RC, Eisenhauer EA, *et al.* Successful re-treatment with taxol after major hypersensitivity reactions. *J Clin Oncol* 1993;11:885–90.
- 17 Zanotti KM, Markman M. Prevention and management of antineoplastic-induced hypersensitivity reactions. *Drug Saf* 2001;24:767–79.
- 18 Szebeni J, Muggia FM, Alving CR. Complement activation by Cremophor EL as a possible contributor to hypersensitivity to paclitaxel: an in vitro study. *J Natl Cancer Inst* 1998;90:7.
- 19 Weiszhar Z, Czucz J, Revesz C, *et al.* Complement activation by polyethoxylated pharmaceutical surfactants: Cremophor-EL, Tween-80 and Tween-20. *Eur J Pharm Sci* 2012;45:492–8.
- 20 Prieto Garcia A, Pineda de la Losa F. Immunoglobulin E-mediated severe anaphylaxis to paclitaxel. *J Invest Allergol Clin Immunol* 2010;20:170–1.
- 21 Madrigal-Burgaleta R, Berges-Gimeno MP, Angel-Pereira D, *et al.* Hypersensitivity and desensitization to antineoplastic agents: outcomes of 189 procedures with a new short protocol and novel diagnostic tools assessment. *Allergy* 2013;68:853–61.
- 22 Gastaminza G, de la Borbolla JM, Goikoetxea MJ, *et al.* A new rapid desensitization protocol for chemotherapy agents. *J Invest Allergol Clin Immunol* 2011;21:108–12.
- 23 Markman M, Kennedy A, Webster K, *et al.* Clinical features of hypersensitivity reactions to carboplatin. *J Clin Oncol* 1999;17:1141.
- 24 Schwartz JR, Bandera C, Bradley A, *et al.* Does the platinum-free interval predict the incidence or severity of hypersensitivity reactions to carboplatin? The experience from Women and Infants' Hospital. *Gynecol Oncol* 2007;105:3.
- 25 Shepherd GM. Hypersensitivity reactions to chemotherapeutic drugs. *Clin Rev Allergy Immunol* 2003;24:253–62.
- 26 Sento T, Sakai N, Itoh Y, *et al.* Incidence and risk factors for paclitaxel hypersensitivity during ovarian cancer chemotherapy. *Cancer Chemother Pharmacol* 2005;56:91–6.
- 27 Hesterberg PE, Banerji A, Oren E, *et al.* Risk stratification for desensitization of patients with carboplatin hypersensitivity: clinical presentation and management. *J Allergy Clin Immunol* 2009;123:1262–7 e1.
- 28 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;19:3126–9.
- 29 Markman M, Zanotti K, Peterson G, *et al.* Expanded experience with an intradermal skin test to predict for the presence or absence of carboplatin hypersensitivity. *J Clin Oncol* 2003;21:4611–4.
- 30 Pagani M, Bonadonna P, Senna GE, *et al.* Standardization of skin tests for diagnosis and prevention of hypersensitivity reactions to oxaliplatin. *Int Arch Allergy Immunol* 2008;145:54–7.
- 31 Garufi C, Cristaudo A, Vanni B, *et al.* Skin testing and hypersensitivity reactions to oxaliplatin. *Ann Oncol* 2003;14:497–8.
- 32 Meyer L, Zuberbier T, Worm M, *et al.* Hypersensitivity reactions to oxaliplatin: cross-reactivity to carboplatin and the introduction of a desensitization schedule. *J Clin Oncol* 2002;20:1146–7.
- 33 Caiado J, Venemalm L, Pereira-Santos MC, *et al.* Carboplatin-, oxaliplatin-, and cisplatin-specific IgE: cross-reactivity and value in the diagnosis of carboplatin and oxaliplatin allergy. *J Allergy Clin Immunol Pract* 2013;1:494–500.
- 34 Leguy-Seguin V, Jolimoy G, Coudert B, *et al.* Diagnostic and predictive value of skin testing in platinum salt hypersensitivity. *J Allergy Clin Immunol* 2007;119:726–30.
- 35 Castells MC, Tennant NM, Sloane DE, *et al.* Hypersensitivity reactions to chemotherapy: outcomes and safety of rapid desensitization in 413 cases. *J Allergy Clin Immunol* 2008;122:574–80.
- 36 Simons FE, Arduoso LR, Bilo MB, *et al.* International consensus on (ICON) anaphylaxis. *World Allergy Organ J* 2014;7:9.
- 37 Muraro A, Roberts G, Worm M, *et al.* Anaphylaxis: guidelines from the European Academy of Allergy and Clinical Immunology. *Allergy* 2014;69:1026–45.
- 38 Lee CW, Matulonis UA, Castells MC. Rapid inpatient/outpatient desensitization for chemotherapy hypersensitivity: standard protocol effective in 57 patients for 255 courses. *Gynecol Oncol* 2005;99:393–9.
- 39 Breslin S. Cytokine-release syndrome: overview and nursing implications. *Clin J Oncol Nurs* 2007;11(1 Suppl):37–42.
- 40 Markman M, Kennedy A, Webster K, *et al.* Paclitaxel-associated hypersensitivity reactions: experience of the gynecologic oncology program of the Cleveland Clinic Cancer Center. *J Clin Oncol* 2000;18:102–5.
- 41 Polyzos A, Tsavaris N, Kosmas C, *et al.* Hypersensitivity reactions to carboplatin administration are common but not always severe: a 10-year experience. *Oncology* 2001;61:129–33.
- 42 Dizon DS, Sabbatini PJ, Aghajanian C, *et al.* Analysis of patients with epithelial ovarian cancer or fallopian tube carcinoma retreated with cisplatin after the development of a carboplatin allergy. *Gynecol Oncol* 2002;84:378–82.
- 43 Brandi G, Pantaleo MA, Galli C, *et al.* Hypersensitivity reactions related to oxaliplatin (OHP). *Br J Cancer* 2003;89:477–81.
- 44 Trudeau ME, Eisenhauer EA, Higgins BP, *et al.* Docetaxel in patients with metastatic breast cancer: a phase II study of the National Cancer Institute of Canada-Clinical Trials Group. *J Clin Oncol* 1996;14:422–8.
- 45 Gennari A, Salvadori B, Tognoni A, *et al.* Rapid intravenous premedication with dexamethasone prevents hypersensitivity reactions to paclitaxel. *Ann Oncol* 1996;7:978–9.
- 46 Markman M, Kennedy A, Webster K, *et al.* Simplified regimen for the prevention of paclitaxel-associated hypersensitivity reactions. *J Clin Oncol* 1997;15:3517.
- 47 Rosenberg P, Andersson H, Boman K, *et al.* Randomized trial of single agent paclitaxel given weekly versus every three weeks and with peroral versus intravenous steroid premedication to patients with ovarian cancer previously treated with platinum. *Acta Oncol* 2002;41:418–24.
- 48 Chouhan JD, Herrington JD. Single premedication dose of dexamethasone 20 mg IV before docetaxel administration. *J Oncol Pharm Pract* 2011;17.
- 49 Syrigou E, Damos I, Kotteas E, *et al.* Hypersensitivity reactions to docetaxel: retrospective evaluation and development of a desensitization protocol. *Int Arch Allergy Immunol* 2011;156:320–4.
- 50 Pagani M, Venemalm L, Bonnadona P, *et al.* An experimental biological test to diagnose hypersensitivity reactions to carboplatin: new horizons for an old problem. *Jpn J Clin Oncol* 2012;42:347–50.
- 51 Kopley CL. Antigen-induced reduction in mast cell and basophil functional responses due to reduced Syk protein levels. *Int Arch Allergy Immunol* 2005;138:11.
- 52 Shalit M, Levi-Schaffer F. Challenge of mast cells with increasing amounts of antigen induces desensitization. *Clin Exp Allergy* 1995;25:896–902.
- 53 Liu A, Fanning L, Chong H, *et al.* Desensitization regimens for drug allergy: state of the art in the 21st century. *Clin Exp Allergy* 2011;41:1679–89.
- 54 Fishman A, Gold T, Goldberg A, *et al.* Effective desensitization protocol to paclitaxel following hypersensitivity reaction. *Int J Gynecol Cancer* 1999;9:156–9.
- 55 Essayan DM, Kagey-Sobotka A, Colarusso PJ, *et al.* Successful parenteral desensitization to paclitaxel. *J Allergy Clin Immunol* 1996;97(1 Pt 1):42–6.
- 56 Sampson HA, Munoz-Furlong A, Campbell RL, *et al.* Second symposium on the definition and management of anaphylaxis: summary report—Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *Ann Emerg Med* 2006;117:7.
- 57 Rueff F, Przybilla B, Bilo MB, *et al.* Predictors of severe systemic anaphylactic reactions in patients with Hymenoptera venom allergy: importance of baseline serum tryptase—a study of the European Academy of Allergy and Clinical Immunology Interest Group on Insect Venom Hypersensitivity. *J Allergy Clin Immunol* 2009;124:1047–54.
- 58 Breslow RG, Caiado J, Castells MC. Acetylsalicylic acid and montelukast block mast cell mediator-related symptoms during rapid desensitization. *Ann Allergy Asthma Immunol* 2009;102:155–60.
- 59 Joint Task Force on Practice P, American Academy of Allergy A, Immunology, *et al.* Drug allergy: an updated practice parameter. *Ann Allergy Asthma Immunol* 2010;105:259–73.
- 60 de Groot H, Mulder WM. Clinical practice: drug desensitization in children. *Eur J Pediatr* 2010;169:1305–9.

Answers

1. A. False; B. True; C. False; D. True
2. False
3. True
4. A. True; B. True; C. False; D. True



Evaluation and management of hypersensitivity reactions to chemotherapy agents

Elizabeth Huiwen Tham, Yew Kuang Cheng, Miah Hiang Tay, Ana Patricia Alcasabas and Lynette Pei-Chi Shek

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