

Immediate Type Hypersensitivity to Chemotherapeutic Agents in Pediatric Patients

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SUMMARY Nine patients (3 boys and 6 girls) with a median age of 9.5 years, with immediate type hypersensitivity reactions to chemotherapeutic agents were reviewed. The presenting symptoms were urticaria (4/9) and anaphylaxis (5/9). The causative agents were vincristine (2/9), L-asparaginase (2/9), mesna (1/9), cyclosporine (1/9), carboplatin (2/9) and cyclophosphamide (1/9). Three of the five patients with anaphylaxis were changed to alternative chemotherapeutic agents. In two cases alternative drugs were not available and the patients underwent safe and successful desensitization. Three of the 4 patients with urticaria were successfully exposed to graded challenges with cyclosporine, carboplatin and cyclophosphamide, respectively. In the other case with generalized urticaria, mesna was withdrawn due to a positive intradermal test. In patients with immediate type hypersensitivity reactions to chemotherapeutic drugs, if effective alternative chemotherapeutic agents are not available and/or the skin test is negative, a careful drug challenge and/or desensitization should be performed.

Immediate type hypersensitivity reactions (IHSRs) have been reported for most of chemotherapeutic agents. The rate of IHSRs in patients receiving multiple doses of chemotherapeutic agents has increased.¹⁻³ The clinical features of IHSRs and their severity are variable and unpredictable. Symptoms can be mild to moderate, such as pruritus, urticaria, facial flushing, erythematous rash, dizziness, diarrhea, facial or lingual swelling, tachycardia, hypotension, hypertension, or severe, such as chest pain, angina pectoris, bronchospasm, anaphylaxis, respiratory arrest, and death.^{4,5}

The exact mechanism is unknown, but several main mechanisms are proposed. Early-onset symptoms are thought to be a result of immediate IgE-mediated hypersensitivity (type I hypersensitivity) or direct histamine release (non IgE-mediated hypersensitivity).^{1,6,7} Bronchospasm, cutaneous

symptoms, and severe hypotension are usually absent in non IgE-mediated reactions. These are best explained by a massive release of TNF-alpha and IL-6 during an episode of symptoms.¹ The non-IgE-mediated reactions do not usually require discontinuation of the chemotherapy because they can be prevented by pre-medications and slower infusions.^{1,8} In addition to IHSRs, a few cases of type II immunologic thrombocytopenia⁹ and type III delayed vasculitic urticaria¹⁰ have been described. Serious immediate IgE-mediated hypersensitivity such as anaphylaxis, generalized urticaria and angioedema requires discontinuation of the drugs or a change to other effective chemotherapeutic agents. If chemo-

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therapy is necessary and alternative agents are not available, desensitization should be the treatment of choice.

When a patient becomes sensitized to a chemotherapeutic agent, physicians are then faced with the decision of whether to discontinue the therapy or risk a re-challenge with the same agent.^{1,3, 5,11-15} There are no reliable risk factors accurately predicting IHSRs to chemotherapeutic agents.⁸ It is important to develop a strategy for the management of such patients. The aim of this study was to review pediatric cases with immediate type hypersensitivity reactions to chemotherapeutic drugs and to propose a management plan.

MATERIALS AND METHODS

Patients

The study was approved by the Ethics Committee, Siriraj Hospital. The medical records of children with immediate type hypersensitivity reactions to chemotherapeutic agents admitted to the Department of Pediatrics, Faculty of Medicine, Siriraj Hospital, Mahidol University, Thailand from January 2004 - December 2006 were reviewed after their parents signed an informed consent. The demographic data, characteristics of the hypersensitivity reactions, skin test results and management were reviewed. The patients were followed for signs of further hypersensitivity after treatment adjustment until December 2008.

Skin testing procedure

A skin prick test (SPT) with the chemotherapeutic agent suspected of causing the hypersensitivity reaction was performed. If the SPT was negative an intradermal skin test (IDT) with 0.02 ml of the chemotherapeutic agent was performed on the volar surface of the other arm. A positive control with 0.02 ml of a 10 mg/ml histamine solution and a negative control with 0.02 ml normal saline solution were performed at the same time. The skin test responses were recorded after 15 minutes and considered positive if the wheal diameters were at least half of the diameters produced by the histamine control and at least 3 mm greater than that of the negative control. The IDT results were considered posi-

tive if the wheal was greater than 5 mm with a surrounding flare.¹⁶ Skin prick tests with vincristine were not performed due to possible local irritation.

Drug challenge and desensitization

The challenges and desensitizations were conducted in the medical intensive care unit (ICU) according to established safety guidelines. Informed consents regarding the potential risks as well as the benefits were obtained before all challenges and desensitizations. Rescue medications including epinephrine, antihistamines, bronchodilators, and supplemental oxygen were prepared in case of anaphylaxis. Patients received pre-medication with an antihistamine such as diphenhydramine 25 mg intravenously 30 minutes before the initiation of the challenge or desensitization. The infusion rate during the challenge or desensitization was doubled every 15 minutes. Hypersensitivity reactions were diagnosed using clinical criteria described by previous studies.^{17, 18} Whenever definite signs or symptoms of hypersensitivity reactions were noted, the chemotherapeutic agents were discontinued and rescue medications were administered. Patients were evaluated continuously for signs and symptoms of hypersensitivity reactions from the beginning of the skin test to 30 minutes after the infusion of the chemotherapeutic agents was completed.

RESULTS

The medical records of 9 patients (3 with acute lymphoblastic leukemia (ALL), 2 with optic glioma, 2 with systemic lupus erythematosus (SLE), 1 with oligodendroglioma and 1 with pure red cell aplasia) who had IHSRs to chemotherapeutic agents were reviewed. The presenting symptoms were urticaria in 4 cases and anaphylaxis in 5 cases. The drugs causing the hypersensitivity reactions were vincristine (VCR), L-asparaginase (L-asp), mesna, cyclosporine, carboplatin and cyclophosphamide (CTX). All patients had received at least one course of the chemotherapeutic agent which was suspected to have caused the IHSR. The demographic data, underlying diseases, characteristics of hypersensitivity reactions, skin test results and management are shown in Table 1. All 9 cases suffered from urticaria. Three cases had generalized urticaria as the only symptom of hypersensitivity. One child had urticaria

Table 1 Characteristics, investigation and treatment of children with hypersensitivity reactions to chemotherapeutic agents

Patient No.	Age (years)	Underlying disease	Drugs	Number of treatment courses	Onset of reactions (minutes)	Symptoms	SPT results	IDT results	Challenge results	Desensitization results	Treatment
1	7	SLE	Mesna	5	10	Urticaria	Neg	Pos	ND	ND	Stop mesna
2	7	SLE	CTX	5	10	Urticaria	Neg	Neg	Neg	ND	CTX
3	14	Oligodendroglioma	Carboplatin	6	5	Urticaria, Nausea, vomiting	Neg	Neg	Neg	ND	Carboplatin
4	12	Glioma	Carboplatin	2	30	Anaphylaxis, Urticaria, hypotension	ND	ND	ND	ND	Actinomycin
5	12	Glioma	VCR	2	40	Anaphylaxis, Urticaria, hypotension	ND	ND	ND	Neg	VCR
6	8	ALL	VCR	2	40	Anaphylaxis, urticaria, hypotension	ND	ND	ND	Neg	VCR
7	2	Pure red cell aplasia with BMT	Cyclosporine	2	10	Urticaria	Neg	Neg	Neg	ND	Cyclosporine
8	7	ALL	L-asp	3	10	Anaphylaxis, Urticaria, chest tightness, abdominal pain	ND	ND	ND	ND	VCR
9	5	ALL	L-asp	5	10	Anaphylaxis, Urticaria, chest tightness, abdominal pain	ND	ND	ND	ND	VCR

SPT, skin prick tests; IDT, intradermal tests; SLE, systemic lupus erythematosus; ALL, lymphoblastic leukemia; ND, not done; Neg, negative; Pos, positive. BMT, bone marrow transplantation; CTX, cyclophosphamide; VCR, vincristine; L-asp, L-asparaginase.

with GI symptoms (nausea and vomiting) which might have been side effects of the drug. Five cases were diagnosed with anaphylaxis. Three of them had generalized urticaria with hypotension while the other 2 had generalized urticaria with chest tightness and abdominal cramps.

Patients no. 1 and no. 2

Two 7-year-old girls with fever, arthralgia and anemia were diagnosed with SLE. Mesna and CTX were given monthly. Both patients tolerated the previous courses without adverse reactions. On the fifth course, they developed generalized urticaria 10 minutes after the initiation of the drug infusion. SPT and IDT were performed with concentrations of 1:100, 1:10 and 1:1 dilution of the suspected drugs, respectively.¹⁹ The first patient had a positive IDT test to mesna at a dilution of 1:10. The diagnosis was mesna hypersensitivity type 1 and it was withdrawn from the treatment schedule. High dose monthly CTX was continued without any reactions. The second patient had a negative SPT and IDT to CTX. A graded challenge with CTX was performed without any reaction. CTX was safely administered in the subsequent courses of treatment.

Patient no. 3

A 14-year-old boy presented with 6 months of headache, nausea and vomiting. Oligodendroglioma was diagnosed from brain tissue biopsies. He was treated weekly with VCR and carboplatin. During the sixth course of treatment, he developed nausea, vomiting and urticaria at the injection site after 5 minutes of carboplatin administration. SPT with 10 mg/ml^{20,21} and IDT with 0.02 ml of 0.1, 1, 10 mg/ml carboplatin^{3,22,23} were performed on the volar surface of the forearm with negative results. Carboplatin desensitization was conducted as suggested by a previous report²⁰ and was completed uneventfully. After that he received carboplatin weekly without any hypersensitivity reactions.

Patient no. 4

A 12-year-old girl presented with recurrent loss of vision. The pathological diagnosis from an optic nerve biopsy showed a low grade glioma. VCR and carboplatin were administered weekly. During the second course of carboplatin (IV infusion

over 60 minutes), she developed urticaria and hypotension 30 minutes after completion of administration. The diagnosis was carboplatin anaphylaxis. Because of the availability of an effective alternative agent, SPT, IDT and carboplatin challenge test were not performed. Carboplatin was replaced by actinomycin.

Patients no. 5 and no. 6

A 12-year-old boy with a low grade glioma and an 8-year-old girl with ALL were treated weekly with VCR. On the second course of VCR, they developed urticaria and hypotension. Due to a lack of effective alternative agents, VCR desensitization was performed and was completed uneventfully. They received VCR weekly without any hypersensitivity reactions until the last course of treatment.

Patient no. 7

A 2-year-old girl was diagnosed with pure red cell aplasia at the age of 8 months. She underwent bone marrow transplantation (BMT) followed by a course of cyclosporine. The patient developed generalized urticaria 10 minutes after the second course of cyclosporine and was successfully treated with chlorpheniramine injections. Since cyclosporine was essential for the prevention of GVHD and there were no effective alternative medicines, a graded challenge with cyclosporine was performed after negative SPT and IDT and was completed uneventfully. Cyclosporine administration was continued for 1 year without any hypersensitivity reactions.

Patients no. 8 and no. 9

A 5- and a 7-year-old boy with ALL received chemotherapeutic agents according to the standard therapeutic protocol. The protocol contained 4 phases: 1) induction phase (L-asp 800 U intramuscular 3 times/week, at weeks 2 and 3), 2) maintenance phase (10 weeks without L-asp), 3) CNS prophylaxis with irradiation, and 4) delay-intensification phase (with L-asp). Ten minutes after the administration of L-asp in the delay-intensification phase, both developed urticaria, chest tightness and abdominal pain. Anaphylaxis to L-asp was diagnosed. L-asp was replaced by VCR, another effective alternative agent, without any reactions.

All patients tolerated the alternative agents or the desensitization/ graded challenge without any hypersensitivity reaction. The chemotherapeutic treatment continued without any hypersensitivity reaction during the follow-up period until December 2008.

DISCUSSION

Immediate type hypersensitivity reactions (IHSRs) to chemotherapeutic agents are not uncommon. The reaction can be caused by the rapid release of preformed and newly formed mediators from sensitized mast cells through the cross-linking of FcεRI by drug allergens.²⁴ It can also be a non-IgE mediated mechanism. However, there is now strong evidence that anaphylactoid reactions are amendable to treatment with the same rapid protocol as for type I hypersensitivity reactions.²⁵

In our study we found 9 children with IHSRs to chemotherapeutic agents over 3 years. These IHSRs did not occur during the first course but after a few courses of treatment. This finding was similar to previous studies^{1,11,14} showing that a long latency is common in chemotherapeutic hypersensitivity. One out of four patients with urticaria had a positive IDT to mesna. Mesna is not a chemotherapeutic agent but a drug for the prevention of hemorrhagic cystitis which is a common side effect of CTX. The other 3 patients with urticaria had negative skin tests to CTX, carboplatin and cyclosporine and also had negative challenges to those drugs. The value of skin tests (SPT and IDT) in investigating IHSRs to chemotherapeutic agents was also confirmed by previous studies.^{1,26,27} It was shown that a negative carboplatin skin test result put the patient at a low risk of anaphylaxis.²² The ideal treatment for patients with IHSRs is to use effective alternative chemotherapeutic agents. If the clinical symptoms of IHSRs are mild or there are no available alternative agents, SPT and IDT should be performed to rule out an IgE-mediated reaction.^{26,27} If the skin test is negative, drug challenge or desensitization should be done. For the patient's safety, these procedures should be performed with special care in an ICU.

Three of our patients who had anaphylaxis received alternative chemotherapeutic agents. In these cases, it was not necessary to perform a skin test or desensitization. In 2 cases with anaphylaxis

there were no effective alternative agents so skin tests with the suspected agents were performed. After SPT and IDT were negative, careful desensitization was done in the ICU. A graded challenge should be done in patients unlikely to have IgE-mediated reaction to drugs. It does not modify an individual's immune response to a given agent. In contrast to the graded challenge, desensitization modifies the immune response to that drug. If the clinical presentation is severe such as anaphylaxis, desensitization can be used for both, the diagnosis of type-I hypersensitivity reactions as well as for treatment. In our study, two patients with VCR anaphylaxis had negative result upon desensitization. This may be explained by a non IgE-mediated mechanism or by modification of the immune response through desensitization.²⁸ Both patients were able to tolerate VCR in the subsequent courses with pre-medication and slow infusion.

In our study, both cases with IHSRs to L-asparaginase suffered from anaphylaxis. A previous study showed that a small-dose test did not predict later L-asparaginase hypersensitivity reactions. If a patient with a serious reaction has to use L-asparaginase, desensitization, changing to the polyethylene glycolated form of the drug, or changing from the common *E. coli* form to the *Erwinia* product is advised.² A recent study showed that premedication and desensitization with *E. coli*-asparaginase could be tolerated in more than half of the cases with L-asparaginase anaphylaxis.²⁹ This study also stated that IHSRs to VCR were very rare but in our study we found 2 cases with anaphylaxis to VCR. Desensitization was successfully done in both cases. Carboplatin, a platinum compound, was associated with anaphylactic-like symptoms in 10-27% of patients. The IHSRs were generally occurring after a period of exposure (4-6 courses of drug administration).² Skin testing has been used to identify patients at risk of developing carboplatin reactions, and a negative test result has been shown to have an extremely high (96%) negative predictive value.²² A skin test is generally performed before administration of a subsequent dose of a suspected agent if the duration between the doses is a week or more as recommended by a previous study.⁸ Skin tests with VCR are not performed because it can irritate the skin at the test area which might obscure the test result. A previous study showed that VCR had vesicant cytostatic toxicity to the skin.³⁰

All 5 patients who required desensitization or a challenge showed no reactions to the procedures. A previous study with a larger study population showed reactions from desensitization and challenges in 33 % (27 % mild and 6 % severe) of the population. However, all reactions were less severe than the initial reactions.³¹

After following the cases until the end of their chemotherapeutic courses, or December 2008, we found that there were no reactions in the subsequent courses of treatment. All cases who received desensitization or a graded challenge received the same methods of chemotherapeutic infusion and antihistamine pre-medication throughout the whole course of their treatment.

After reviewing the pediatric patients with immediate type hypersensitivity to chemotherapeutic

agents, we recommend the schedule shown in Fig. 1. In patients with anaphylaxis, the hypersensitivity agents should be withdrawn and effective alternative chemotherapeutic agents should be administered if available. If alternative agents are not available, skin tests with the suspected drugs should be performed. If the skin tests are negative or cannot be done, desensitization should be carefully performed. If the skin tests are positive, the agent should be withdrawn. In case that the agent is necessary for the treatment, desensitization should be very carefully performed. The desensitization should be carried out in an ICU for safety reasons. In patients without anaphylaxis, a graded challenge can be performed safely after negative skin tests.

CONCLUSION

Immediate type hypersensitivity reactions to

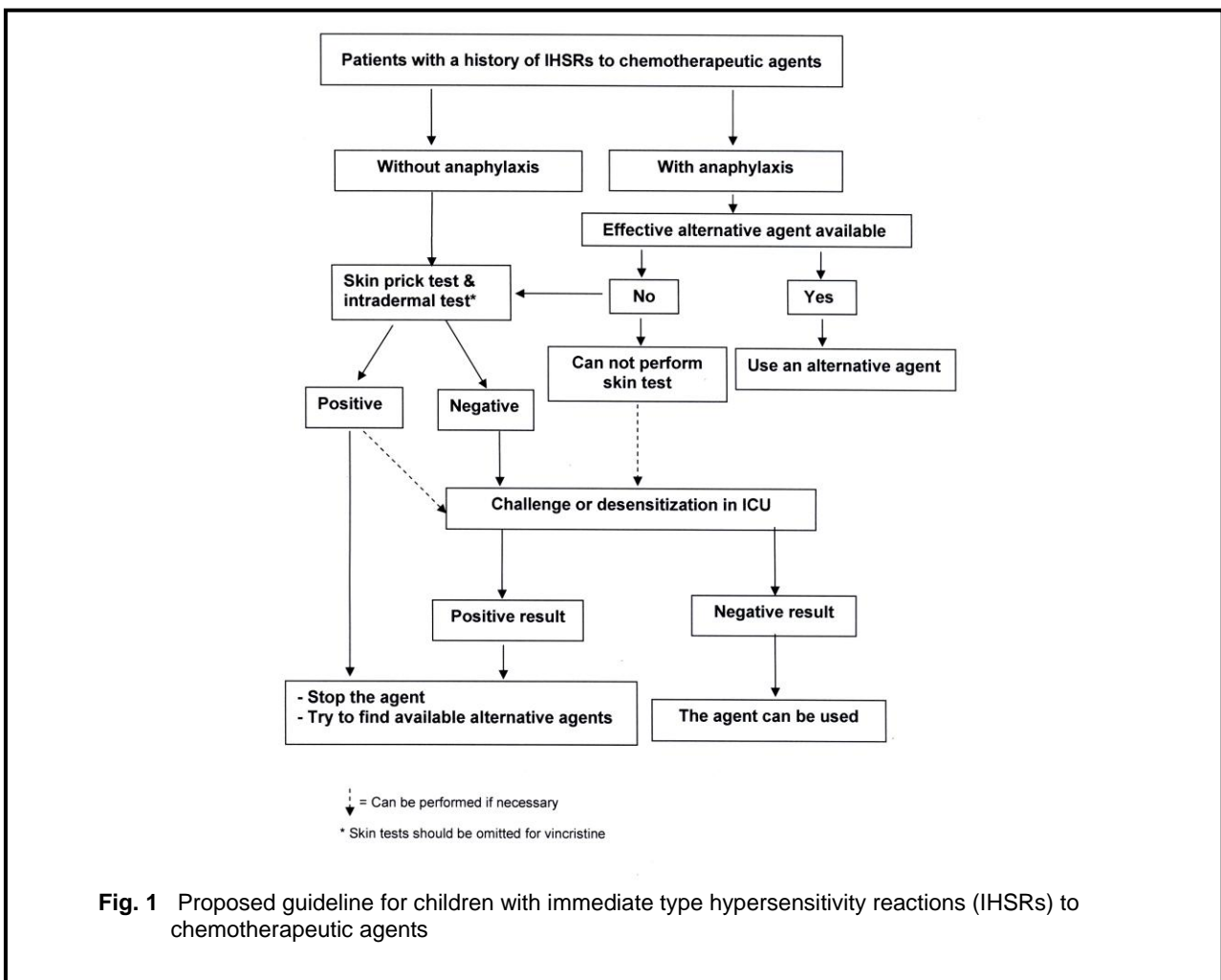


Fig. 1 Proposed guideline for children with immediate type hypersensitivity reactions (IHSRs) to chemotherapeutic agents

chemotherapeutic agents are not uncommon. If effective alternative agents are not available and a skin test to the hypersensitive agents is negative, a careful drug challenge should be performed in non anaphylactic cases and desensitization should be performed in anaphylactic cases.

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