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Successful Desensitization to Carboplatin in Patients With Systemic Hypersensitivity Reactions

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Carboplatin is the drug of choice for the treatment of nonresectable astrocytomas in children, but patients who are intolerant may require cranial irradiation which is associated with significant morbidity. Hypersensitivity reactions, including urticaria, bronchospasm, and hypotension, have been reported in 1% to 30% of patients treated with carboplatin. Although a few patients have attempted to continue therapy following pretreatment with antihistamines and corticosteroids, most have had recurrent severe reactions and have discontinued therapy.

Two children with a history of severe systemic reactions to carboplatin were pretreated with 1 to 2 mg/kg of oral prednisolone the night before and the morning of their infusion. The initial desensitization was carried out in the intensive care unit (ICU) using doses of 1, 2.5, 5, 10, 25, and 50 mg of carboplatin infused at 1 mg/min every 15 minutes. This was well-tolerated and the remainder of the dose was infused at the standard rate of 200 mg/hr. One patient continued to receive infusions in the clinic without any difficulty. The other patient tolerated a second infusion, but during his third he experienced a systemic reaction that required discontinuation of the infusion and treatment with diphenhydramine. Desensitization was repeated in the ICU with pretreatment with prednisolone, diphenhydramine, and ranitidine, starting with 0.1 mg of carboplatin, and increasing more slowly than in the first protocol. This was well-tolerated, and subsequent infusions have been administered beginning with 1 mg doses without adverse effects. Both boys continued therapy with carboplatin; their astrocytomas are stable and they are clinically well. The use of the desensitization protocol enabled them to avoid cranial irradiation and improved their chances for normal neurologic development.

Key words: carboplatin, hypersensitivity, desensitization, drug allergy, astrocytoma

INTRODUCTION

Carboplatin is active in the treatment of a variety of childhood brain tumors, including pilocytic astrocytoma [1–4]. In general, carboplatin is well-tolerated; the major side effect is bone marrow suppression, particularly thrombocytopenia. It does not have the limiting nephrotoxicity or ototoxicity of the parent drug cisplatin. Hypersensitivity reactions are unusual, but have been reported in adults treated for a variety of malignancies [5] and in up to 30% of children [3,4,6,7]. In nearly all of these patients, the reactions were of sufficient severity that it was necessary to discontinue therapy. For most patients, the alternative treatment is cranial irradiation which can substantially delay tumor progression, but is highly toxic to children, especially those less than three years of age [8–10]. The toxicity of cranial radiotherapy includes intellectual deterioration, endocrine dysfunction, and second malignancy. Other chemotherapeutic agents, including vincristine, actinomycin-D, and cyclophosphamide, have demonstrated activity against pilocytic astrocytoma, but carboplatin appears to be the single best available agent for progressive or recurrent disease [2].

Hypersensitivity reactions to carboplatin in adults include generalized pruritus and erythema, dyspnea, cyanosis, hypotension, hypoxemia, abdominal cramping, tightness in the throat, and chest pain [5]. Adverse reactions to carboplatin were reported in 10 of 150 children undergoing therapy for brain tumors [3,4,6,7]. Reactions included fever, pruritus, erythematous rash, dyspnea, hypotension, and urticaria. All ten patients had to discontinue therapy.

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Some clinicians have attempted to continue therapy in spite of the hypersensitivity reactions, but only a few have been successful [6,11,12]. One patient tolerated an infusion after pretreatment, but despite the premedication experienced severe allergic reaction following the next infusion [5]. Based on this, Weidmann et al. [5] concluded that further therapy should not be attempted in patients who have experienced adverse reactions.

We report two children who experienced severe systemic reactions to carboplatin and have been able to continue therapy using a protocol consisting of slow desensitization combined with premedication.

MATERIALS AND METHODS

Patients

Patient LA is a 3-year-old boy who was diagnosed with astrocytoma at 16 months of age and underwent partial resection. Progressive tumor was resected seven months later. When tumor again progressed, he was treated with carboplatin, 560 mg/m^2 every four weeks, which was well-tolerated for nine months. During the tenth infusion he developed cough and congestion, and during the eleventh infusion he developed cough, flushing, and erythema on his neck. The infusion was discontinued and he was treated with intravenous (i.v.) diphenhydramine.

The second patient, WK, is a 7-year-old boy who was diagnosed with pilocytic astrocytoma at 4 years 5 months of age and underwent surgical resection. One year later, progression was noted, and he was begun on carboplatin 560 mg/m^2 every 4 weeks. During his eight infusion, he developed red macules around his eyebrows. During his ninth infusion he had severe abdominal pain followed by total body erythema. The drug was discontinued, and he was treated with diphenhydramine, hydrocortisone, and epinephrine. Seven months later he underwent another resection for progressive disease. Both boys recovered uneventfully and suffered no permanent injury, but the reactions were sufficiently severe that carboplatin was withheld and the use of radiotherapy contemplated.

Methods

Both intradermal and epicutaneous or prick skin tests were performed using a solution of carboplatin in saline at a concentration of 50 μg/ml. Patient LA was tested at 2 months and patient WK was tested at 8 months following last exposure to carboplatin. Patient LA had no reaction to testing by either method. Patient WK had no reaction upon epicutaneous testing, but did not have intradermal tests placed. He was retested after he reacted to his third infusion, and skin tests remained negative.

The carboplatin for both desensitization and treatment was diluted in D5½NS to a concentration of 1 mg/ml. The desensitization was carried out as indicated in Tables II and III and is discussed in the Results.

TABLE I. Premedication Protocol for Carboplatin Desensitization*

Time before procedure	Medication	Dose (mg/kg po)
12 hr	Prednisolone	1–2
1 hr	Prednisolone	1–2
30 min	Diphenhydramine	1–2
30 min	Ranitidine	2–4

*Diphenhydramine and ranitidine should be used only if patient experiences hypersensitivity reactions despite prednisolone and slow infusion of carboplatin.

TABLE II. Initial Carboplatin Desensitization Protocol

Dose (mg)	Rate		Cumulative dose
1.0	1 mg/min	i.v. push q15 min	1.0
2.5			3.5
5.0			8.5
10			18.5
25	100 mg/hr	Infusion q15 min	43.5
50			93.5
331	200 mg/hr	Continuous infusion	425

RESULTS

Initial Protocol

Both children were pretreated with 1–2 mg/kg oral prednisolone the night before and the morning of their infusion (Table I). The initial desensitization was carried out in the pediatric intensive care unit (ICU). Desensitization was performed using doses of 1.0, 2.5, 5.0, and 10 mg carboplatin infused at 1 mg/min every fifteen minutes, followed by 25 and 50 mg infused at 100 mg/hr (Table II). This was well-tolerated, and the remainder of the dose was infused at the standard rate of 200 mg/hr. No adverse reactions occurred, and both patients had a subsequent infusion in the clinic without difficulty. Patient LA continued to receive carboplatin every 4 weeks according to this protocol without hypersensitivity reaction. Patient WK, however, developed generalized erythema and palmar pruritus during his third course, just after the 10 mg i.v. push. This was followed by swelling of the face and neck which required discontinuation of the infusion and treatment with diphenhydramine.

Subsequent protocols. WK returned to the ICU for subsequent doses of carboplatin. A slower desensitization protocol combined with more intensive premedication was selected. Prick skin test was again negative. He was premedicated with oral prednisolone the night before and the morning of his infusion, and in addition received 25 mg diphenhydramine and 50 mg of ranitidine intravenously immediately prior to desensitization (Table I). Carboplatin was infused at 15-minute intervals beginning with 0.1, 0.2, and 0.5 mg doses, increasing in small increments. He did well until the 10 mg dose when he

TABLE III. Protocol for Desensitization to Carboplatin

Concentration (mg/ml)	Dose[a] (mg)	Cumulative dose (mg)
0.1	0.1	0.1
0.1	0.2	0.3
0.1	0.5	0.8
1.0	1.0	1.8
1.0	1.0	2.8
1.0	2.0	4.8
1.0	2.0	6.8
1.0	3.0	9.8
1.0	4.0	13.8
1.0	5.0	18.8
1.0	7.5	26.3
1.0	10.0	36.3
1.0	15.0	51.3
1.0	100.0 (100 mg/hr)	151.3
1.0	Remainder of of dose (200 mg/hr)	To total dose

[a]Doses are given i.v. push every 15 min at a rate of 1 mg/min up to 15 mg. Time is measured from the end of the proceeding infusion. If the patient does not have an adverse reaction during the first desensitization, subsequent infusions can begin with the 1 mg dose.

developed mild facial erythema without swelling or respiratory distress. This gradually improved without specific therapy, and he received 15 mg over 30 minutes followed by 20 mg at 50 mg/hr and then 30, 40, 50 and 75 mg at 100/hr given at 15 minute intervals. The infusion was completed at 200 mg/hr without further reactions.

Facial flushing did not occur until more than 10 mg were infused, so it was unlikely that the very small doses were necessary. For his fifth desensitization, the protocol was adjusted to desensitize more rapidly and avoid the very small starting doses. The same premedications were given orally; he again received carboplatin doses at 15 minute intervals, but starting at 1 mg (Table III). The protocol was further simplified by beginning a constant infusion of 100 mg at 100 mg/hr immediately after the 15 mg dose, and then completing the infusion at 200 mg/hr, as shown in Table III.

Patient LA completed 12 infusions without any reactions. His tumor remained stable and he experienced no further hypersensitivity reactions, but the carboplatin was discontinued when he developed hearing loss. Patient WK has had 27 infusions, 24 with the extended protocols. Both are clinically well. Follow-up MRI scans show no progression of the tumors since resuming carboplatin.

DISCUSSION

Continuation of therapy with drugs such as penicillin and insulin, as well as the use of radiocontrast dyes, has been possible in patients who experience hypersensitivity reactions to these agents. The pathophysiology of adverse reactions to these drugs differs, and thus the procedures for avoiding these reactions also differ. The hypersensitivity reactions to penicillin and insulin are thought to be classical IgE-mediated allergic reactions [13]. These reactions require presensitization and may occur in a sensitized individual after only microgram quantities are infused. These agents induce true anaphylactic reactions including urticaria, angioedema, wheezing, dyspnea, and hypotension. The presence of IgE-mediated sensitivity usually can be detected in vivo by skin testing or in vitro by radioallergosorbent tests (RAST), but such testing has limited usefulness in drug allergy because most drugs are of low molecular weight and are not immunogenic in the native form [14]. Desensitization protocols are based on the administration of extremely small, often submicrogram doses which are slowly increased over several hours [15]. This procedure is thought to consume IgE antibodies slowly and in a controlled manner. Occasionally patients are pretreated with antihistamines and/or corticosteroids, but pretreatment is seldom necessary.

In contrast, in susceptible patients other drugs, including radiocontrast dyes, opiates, muscle relaxants, and plasma expanders, are thought to act directly on mast cells to induce the release of mediators such as histamine, prostaglandin PGD_2, and leukotriene LTC_4 [16]. Since a reaction may occur on first exposure to these agents, it would seem that prior sensitization is not required. These reactions also differ from IgE-mediated reactions in that they usually required larger quantities of the drug to induce symptoms. They induce anaphylactoid reactions that clinically are similar to the reactions induced by penicillin and may be severe, even life-threatening. Anaphylaxis-like reactions may also be mediated by formation of immune complexes and subsequent activation of complement. Anaphylatoxins C3a and C5a are generated, leading to increased vascular permeability and the release of mediators from mast cells and basophils [17]. Reactions may be prevented by pretreatment with corticosteroids and either an H1 antihistamine or a combination of H1 and H2 antihistamines [15,17].

The mechanisms of adverse reactions to carboplatin are unknown. These reactions are anaphylactic or anaphylactoid in nature and usually occur after several courses of therapy, suggesting presensitization such as with penicillin. They occur late in the infusion, however, unlike the typical IgE-mediated reactions and more like those induced by radiocontrast dyes. Studies do not consistently demonstrate the presence of IgE antibody *in vivo* or in vitro [5,12]. Only one patient, a woman treated for adenocarcinoma of the ovary, has been evaluated in any detail [12]. She had been treated previously with the parent drug cisplatin, and on investigation was found to have positive intradermal skin tests to carboplatin and positive prick and intradermal skin tests to cisplatin. Prick skin tests to carboplatin were negative. Serum IgE

one month after her anaphylactic event was 646 ng/ml and declined to 88 ng/ml by four months. No specific IgE to carboplatin was demonstrated in vitro on RAST testing, and carboplatin did not induce release of histamine in basophils exposed to patient's serum. A positive control was not available, however, for these in vitro tests.

In the study be Weidmann et al. [5], two adults with systemic reactions to carboplatin had no reaction when skin-tested by the prick technique using a solution of carboplatin at a concentration of 10 mg/ml, but both reacted to an intracutaneous injection of 0.01 ml of 1 mg/ml solution. Control subjects who had been treated with carboplatin but had not experienced adverse reactions did not have positive skin tests. Neither of our patients had positive prick skin tests with a solution of carboplatin at 50 μg/ml. One of the boys was also negative to an intracutaneous injection of the same solution. Repeat skin testing after reexposure was still negative, even after another systemic reaction. Thus, we were unable to document the presence of IgE antibodies to carboplatin. Indeed, since relatively high concentrations of carboplatin were required to evoke systemic reactions, it is more likely that this drug acts like a direct mast cell releasing agent.

Previous attempts at desensitization have been only partially successful (Table IV). One woman who had experienced generalized pruritus was able to receive two more courses of carboplatin with prophylactic steroids and antihistamines [11]. Another patient, who despite pretreatment with corticosteroids and antihistamines had complained of perioral tingling, palmar pruritus, and dyspnea, and then became ashen, cyanotic, hypotensive, and hypovolemic, was able to complete four additional courses of carboplatin by utilizing a desensitization protocol consisting of hourly injections of 0.35 mg, 3.5 mg, and 35 mg, followed by the remainder of her dose over 1 hour [12]. Two of three patients who experienced systemic symptoms to carboplatin, including palmar erythema, dyspnea, or collapse, were able to continue therapy following pretreatment with hydrocortisone and chlorpheniramine [18]. One 57-year-old man who experienced a systemic reaction to carboplatin tolerated one infusion after pretreatment with prednisolone and antihistamines, but despite premedication experienced severe allergic reactions following the next infusion [5]. Premedication was similarly unsuccessful in allowing a 45-year-old woman with severe systemic reactions to continue therapy [19].

In a report of one child who had developed hives to cisplatin [6], premedication with diphenhydramine and hydrocortisone prior to each dose of carboplatin enabled him to complete four doses at 100 mg/m^2 without allergic reaction, but upon increasing to 175 mg/m^2 he developed severe hives, requiring discontinuation of carboplatin. In another study of six children, four of whom had severe anaphylactic reactions, pretreatment of one patient with diphenhydramine and prednisolone and a slower infusion rate prevented symptoms during the next four infusions [7]. The drug was discontinued, however, when dyspnea and hypotension occurred during the fifth infusion.

In our report, patient LA was able to continue carboplatin therapy without premedication with antihistamines by using a slow desensitization protocol. It was assumed that he retained his sensitivity to carboplatin; thus, the desensitization was repeated prior to each infusion. It is possible, however, that he has lost reactivity, but this cannot be determined without challenging him with a standard infusion. There is no test for sensitivity that is sufficiently sensitive or specific. The second child, WK, was more sensitive to carboplatin, but tolerated subsequent infusions by pretreatment with antihistamines and a slow desensitization protocol. Although a less conservative protocol might suffice, the risk of developing a severe reaction would be greater. Pretreatment with antihistamines was not used in the initial protocol because it can mask the early signs of anaphylaxis and necessitates very careful observation during the treatment period. WK's protocol was shortened in several stages based on his lack of clinical symptoms, so that the current procedure can be completed in less than 10 hours.

CONCLUSIONS

Although the mechanisms of adverse reactions to carboplatin are unknown, desensitization in combination with premedication has enabled these two patients to continue carboplatin treatment and avoid cranial radiotherapy. It is possible that a shorter protocol might be sufficient for some patients, but in light of the severity of these reactions and the failure of most attempts to continue therapy, it is justified to be conservative and desensitize slowly. This form of desensitization may not permanently alter the hypersensitivity state; therefore, the patient must be desensitized for each course of carboplatin therapy. Even if the infusions are given weekly [7], a state of hyporesponsiveness would not necessarily persist, so that desensitization would still be needed with each infusion. Pretreatment with antihistamines may prevent allergic reactions, but may also mask early signs of anaphylaxis such as pruritus. Thus, if patients who have experienced hypersensitivity reactions are pretreated with antihistamines, desensitization should be performed in a setting where emergency care is readily available. The use of antihistamines to prevent allergic symptoms might best be reserved for patients who have not experienced life-threatening reactions.

Because of the risk of severe reactions, initial desensitization therapy should be carried out in an intensive care setting. Desensitization is contraindicated for agents that evoke reactions such as toxic epidermal necrolysis,

TABLE IV. Attempts to Continue Therapy in Patients With Hypersensitivity Reactions to Carboplatin

No. of patients	Reaction	Premedication[a]	Desensitization	Subsequent reactions	Outcome	Reference
1	Generalized pruritus	HC, H1	None	None	Completed 2 infusions	[11]
1	Pruritus, dyspnea, cyanosis, hypotension	Dex, H1	.35, 3.5, and 35 mg inj.	Mild pruritus	Completed 4 infusions	[12]
3	Palmar erythema, dyspnea, collapse	HC, H1	None	2 Patients–none 1 Patient–severe systemic rxn	2 Patients continued 1 Patient discontinued	[18]
1	Flush, nausea and vomiting, diarrhea, sweating, angina	Pred, H1	None	Tolerated 1 infusion; severe reaction to the next	Discontinued	[5]
1	Pruritus, rash, facial edema, cramping	Dex, H1, H2	None	Similar reactions	Discontinued	[19]
1	Severe urticaria	HC, H1	None	Tolerated four doses at 100 mg/M^2, urticaria at 175 mg/M^2	Discontinued	[6]
1	Urticaria, wheezing	Pred, H1	Slow infusion	Dyspnea and hypotension during 5th infusion	Discontinued	[7]

[a]HC, hydrocortisone; Pred, prednisolone; Dex, dexamethasone; H1, H1 antihistamine (e.g., diphenhydramine); H2, H2 antihistamine (e.g. ranitidine, cimetidine).

erythema multiforme, and Stevens-Johnson syndrome because these result from direct toxic effects or involve cell-mediated immune responses. Continued exposure to the drug during these reactions is likely to intensify the immune response and resulting damage. Desensitization protocols should be considered for carboplatin, as well as for a wide variety of other medically necessary drugs that produce immediate systemic adverse reactions.

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