

Safety and efficacy of repeated monthly carboplatin desensitization

To the Editor:

Carboplatin, a second-generation platinum antineoplastic agent, has been reported to cause hypersensitivity reactions. As carboplatin finds increasing applications in clinical practice, the frequency of documented reactions may be rising.¹ Carboplatin hypersensitivity is often heralded by a sudden reaction after multiple uneventful courses; less commonly, platinum-naïve patients have also reacted immediately with the first infusion.² Each separate exposure to carboplatin has been postulated to lower the threshold for development of overt hypersensitivity, which poses a problem because of the frequent need to administer carboplatin repeatedly. Available data suggest that reactions to carboplatin usually recur with the subsequent rechallenge. In 1 series, 3 of every 4 patients rechallenged mounted a similar reaction.³ In another, 2 of every 3 patients reacted after rechallenge.⁴ For this reason, desensitization is recommended if carboplatin is to be readministered after a hypersensitivity reaction has occurred. Successful desensitization procedures have been performed, generally as a one-time desensitization followed by the appropriate number of routine infusions to complete the cycle.⁵ We report successful reduction in tumor size made possible by repeated desensitization performed anew for all subsequent monthly infusions of carboplatin in a child with a hypersensitivity reaction to this drug.

A 4-year-old girl who presented with a pilocytic astrocytoma of the brainstem was being treated with carboplatin (560 mg/m²/dose) and vincristine (1.5 mg/m²/dose) every 4 weeks. Reduction in tumor size was demonstrated by magnetic resonance imaging after the seventh monthly infusion. During the eighth infusion, she developed diffuse flushing and urticaria, facial edema, cough, and subjective chest tightness 25 minutes after initiation. Symptoms resolved after immediate discontinuation of the infusion and treatment with H₁ antihistamines and corticosteroids. She had no other drug hypersensitivity history, a factor that may predict a higher risk of reacting to carboplatin.⁶ Clinically, this type of reaction was consistent with hypersensitivity described for carboplatin, and a desensitization protocol with escalating doses of carboplatin was designed for all subsequent infusions (Table I). Skin testing was not performed, although this has been attempted as an objective tool to predict risk of reactions before infusions.⁷ We feel that skin testing is less helpful once a hypersensitivity reaction has occurred, in which setting desensitization should be attempted regardless of the results of skin testing. Vincristine was continued as before.

The patient tolerated desensitization well but had occasional reactions, mostly mild facial flushing, which were successfully treated with H₁ antihistamines and corticosteroids and were markedly less severe than the

TABLE I. Carboplatin desensitization regimen*

Dose (mg)	Rate (intravenous, every 15 min)	Cumulative dose
1.0	1 mg/min	1.0 mg
2.5	Same	3.5 mg
5.0	Same	8.5 mg
5.0†	Same	13.5 mg
7.5	Same	21.0 mg
7.5†	Same	28.5 mg
10	Same	38.5 mg
10†	Same	48.5 mg
25	100 mg/h	73.5 mg
50	Same	123.5 mg
Remainder	Over a period of 90 min continuously	Total dose‡

*Premedication regimen included cetirizine 10 mg, ranitidine 50 mg, prednisone 2 mg/kg, and montelukast 4 mg (given once the night before and the morning of the desensitization).

†This duplicated dose was added to decelerate the dose build-up as a result of a reaction at this point in the protocol.

‡The total dose was 375 mg for our 18-kg patient.

initial reaction that required cessation of the infusion. To prevent these breakthrough reactions, antihistamines, corticosteroids, and a leukotriene modifier were administered as premedication (Table I). As an additional measure, any dose resulting in breakthrough symptoms was duplicated in lieu of the next scheduled dose, thereby decelerating the rate of build-up; the total dose remained unchanged. Duplicated doses were permanently added at 3 points in the protocol for all subsequent infusions as well, which successfully reduced the incidence of breakthrough reactions. Desensitization during each infusion permitted completion of the entire planned cycle of chemotherapy. Magnetic resonance imaging performed after the last infusion revealed further dramatic and durable reduction in tumor size (Fig 1).

Patients undergoing carboplatin desensitization remain at risk for hypersensitivity reactions during the procedure. In 1 series, 7 of 33 patients undergoing desensitization (with protocols different from ours) had reactions that precluded continuation of carboplatin.⁸ In addition, deaths have occurred after unsuccessful desensitization to carboplatin.⁹ We believe desensitizing anew for each infusion, decelerating the dose escalation by duplicating problematic doses, and managing breakthrough symptoms with antihistamines improved safety and tolerability. Other reported carboplatin protocols have used no premedication, and none have used a leukotriene modifier. Such antihistamine/corticosteroid regimens used for premedication and breakthrough symptoms should be reserved for breakthrough reactions bothersome to the patient but not serious enough to warrant abandoning desensitization.

To our knowledge, this is the first reported case of desensitization repeated for each monthly carboplatin infusion in a pediatric outpatient setting. Management of

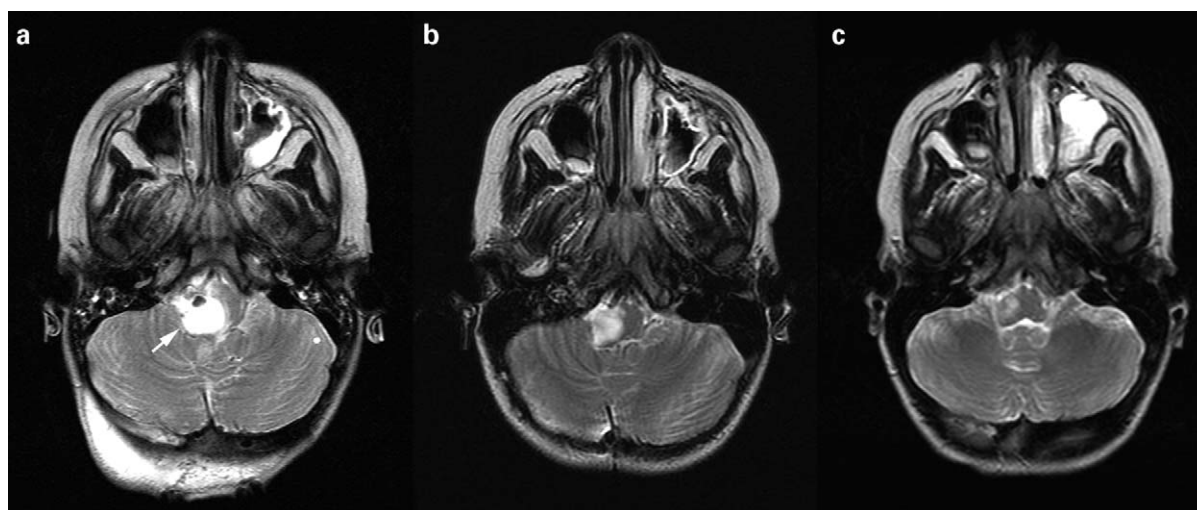


FIG 1. Sequential MRI demonstrating tumor size at baseline (A), at time of development of hypersensitivity (B), and after completion of chemotherapy made possible by desensitization to carboplatin (C).

breakthrough symptoms by premedicating and decelerating the dose escalation successfully improved tolerability. Avoidance of substantial morbidity associated with cranial irradiation and possibility of cure with chemotherapy justify the additional measures and risk involved in desensitizing repeatedly to carboplatin.

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Recurrent anaphylaxis linked to pantoprazole

To the Editor:

Pantoprazole (Protonix/Wyeth-Ayerst, Madison, NJ), the fourth benzimidazole proton pump inhibitor to become available in the United States, has been increasingly used for the oral treatment of gastroesophageal reflux disease. There have been 2 case reports of anaphylactic reactions after administration of pantoprazole.^{1,2} We describe the case of a man with recurrent anaphylaxis induced by pantoprazole and investigate its relationship to cytochrome P450 polymorphisms.

A 47-year-old Hispanic male was referred to our clinic for evaluation of recurrent idiopathic anaphylaxis (urticaria, angioedema, substernal chest discomfort, orthostasis, and impaired consciousness) of 8 months' duration. He had no significant past medical history of atopy, drug allergy, or chronic medical conditions with the exception of gastroesophageal reflux disease treated with intermittent pantoprazole. Previous anaphylactic events occurred sequentially 24, 10, and 4 hours after pantoprazole, each after several days of uneventful use. The history was not compelling for provoking food ingestion, exercise, or another culprit before these episodes. With the exception of cockroach, results of serum IgE measurement to