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Hypersensitivity to Carboplatin in Children

Amalia Schiavetti, MD, Giulia Varrasso, MD, Palma Maurizi, MD, and Manuel A. Castello, MD*

Background. Hypersensitivity reactions are rare but at times severe complications to cytostatic drugs. ***Procedure.*** The percentage of allergic reactions to carboplatin and their clinical features were evaluated in 185 children affected by different solid tumors and treated with etoposide-carboplatin chemotherapy. Allergic reactions that occurred during or immediately following etoposide infusion (5 cases, 2.8%) were excluded from the study. ***Results.*** Seventeen out of 185 patients (9.2%) suffered from allergic responses to carboplatin. The first of these occurred after an average of 10.1 courses (range, 1–23; median, 9). The risk calculated according to the number of courses is 2% at 6 courses, 11.3% at 12 courses, and 47% at more than 12 courses. ***Conclusions.*** The high risk of allergic reactions to multiple courses of carboplatin should be kept in mind when developing treatment regimens that include the drug. Med. Pediatr. Oncol. 32:183–185, 1999.

Key words: carboplatin; hypersensitivity; childhood solid tumors

INTRODUCTION

Hypersensitivity reactions are rare but sometimes life-threatening complications of cytostatic drugs. The majority of reports on carboplatin hypersensitivity have been described in adults. In this study we assess the number and the clinical features of allergic reactions calculated on 185 children treated with carboplatin-based chemotherapy.

PATIENTS AND METHODS

From January 1989 to April 1997, 185 children with different solid tumors were treated with etoposide and carboplatin association. The chemotherapy schedule consisted of Jet Regimen: etoposide (300 mg/sqm as a 1-hr infusion) followed by carboplatin (1,000 mg/sqm as a 3- to 5-hr infusion) on 1 day, every 3–4 weeks; or as an alternative, low-dose Jet Regimen: etoposide (200 mg/sqm as a 1-hr infusion) followed by carboplatin (600 mg/sqm as a 3- to 5-hr infusion) on 1 day, every 3–4 weeks. The children in whom an allergic reaction occurred during or immediately following etoposide infusion (5 cases, 2.8%) were excluded from the study. Seventeen out of 185 patients suffered from allergic reactions to carboplatin (Table I). They received 209 total courses of chemotherapy (mean number of courses per patient, 12.3; range, 1–28). The first reaction occurred after an average of 10.1 courses (range, 1–23; median, 9). In 15 cases the allergic reaction occurred during carboplatin infusion; only in 2 cases was the reaction mild and delayed for 2–3 hr. The cumulative dose of carboplatin at which the first allergic reaction occurred ranged from 600 mg/sqm to 16,700 mg/sqm (average, 6,900 mg/sqm).

No deaths occurred. Clinical symptoms were the result of histamine-induced type I hypersensitivity. In one case macroscopic hematuria was also observed during carboplatin infusion. One patient presented anaphylaxis at the first course. Eleven patients presenting mild reaction received further courses in which carboplatin was administered separately from etoposide (at least 12-hr interval).

RESULTS

In our series the percentage of hypersensitivity to carboplatin was 9.2%. The risk of reaction calculated according to the number of courses was 2% (2 out of 99 patients) at 6 courses, 11.3% (8 out of 71) at 12 courses and 47% (7 out of 15) in patients that received more than 12 courses (Table II). The severity of the reactions was grade 1 in nine cases, grade 2 in three, grade 3 in four, and grade 4 in one according to the toxicity criteria of the National Cancer Institute (Table III).

In 11 patients, 37 further total courses of carboplatin were administered after grade 1 or 2 first reaction and corticosteroid-antihistamine premedication was carried out in 25 courses. We observed 17 allergic reactions (68%) in spite of premedication. In patients with grade 3 and 4 reaction, carboplatin-based chemotherapy was stopped.

Department of Pediatrics, University ''La Sapienza,'' Rome, Italy

*Correspondence to: Manuel A. Castello, MD, Department of Pediatrics, University of Rome ''La Sapienza,'' Viale Regina Elena, 324, Rome 00161, Italy.

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TABLE I. Characteristics of Patients Who Developed Allergic Reaction to Carboplatin*

Patient	Age months	Diagnosis	Number of courses at first reaction	Grade of reaction	Therapy	Number of further courses	Number of total courses
1	136	MB	8	II	Antihistamines	11	19
2	122	MB	18	II	Antihistamines	1	19
3	46	LGA	13	III	Corticosteroids	0	13
4	121	LGA	6	III	Antihistamines	0	6
5	103	MB	19	I	Antihistamines	1	20
6	27	LGA	1	IV	Corticosteroids Adrenaline	0	1
7	82	MB	1	I	Antihistamines	5	6
8	104	MB	12	III	Corticosteroids Antihistamines	0	12
9	85	LGA	7	III	Corticosteroids Antihistamines	0	7
10	112	NB	6	I	Antihistamines	3	9
11	41	NB	10	I	Antihistamines	2	12
12	16	NB	21	I	Antihistamines Corticosteroids	6	27
13	8	RB	23	I	Antihistamines Corticosteroids	5	28
14	8	RB	10	I	Antihistamines	0	10
15	35	RB	9	I	Antihistamines	1	10
16	162	O	7	II	Antihistamines Corticosteroids	1	8
17	189	CA	1	I	Corticosteroids	1	2

*MB, medulloblastoma; LGA, low-grade glioma; NB, neuroblastoma; RB, retinoblastoma; O, osteosarcoma; CA, carcinoma.

TABLE II. Cumulative Risk of Hypersensitivity Reaction With Course Number of Carboplatin

Course number	Number of patients receiving courses	Number of patients with hypersensitivity	Cumulative risk of hypersensitivity (%)
6	99	2	2
6–12	71	8	11.26
>12	15	7	47

TABLE III. Toxicity Scale According to the National Cancer Institute*

Grade 0	None
Grade 1	Transient rash, drug fever <38°C
Grade 2	Urticaria, drug fever >38°C, mild bronchospasm
Grade 3	Serum sickness, bronchospasm, requires parenteral medication
Grade 4	Anaphylaxis

*Ref. 13.

DISCUSSION

In the last few years there have been some reports on carboplatin hypersensitivity in adults [1–10]. Allergic reactions to carboplatin have been described more rarely in children. In phase 1 studies on carboplatin for a wide range of malignancies, hypersensitivity reactions occurred in 2%–4% of the pretreated cases [11,12]. Only in childhood brain tumors was the percentage of hypersensitivity calculated on a large number of cases owing to the fact that repeated courses of carboplatin are most commonly used in this pathology. These reports indicate an incidence of 2%–12% [13–15].

In the present study, hypersensitivity to carboplatin was found in 9.2% of children affected by different solid tumors. Also, etoposide may be responsible for hypersensitivity. The children in whom an allergic reaction occurred during or immediately following etoposide infusion (5 cases, 2.8%) were excluded from the study. We have assumed that hypersensitivity was due to carboplatin in all the patients presenting symptoms during its infusion. Only two patients had delayed hypersensitivity and they were treated again with carboplatin but not immediately after etoposide. The risk of hypersensitivity increases with repeated exposure to carboplatin and is not correlated with a single dose (carboplatin at 1,000 mg/sqm vs. 600 mg/sqm). The percentage, calculated on the number of courses, increases from 2% at 6 courses, to 11.3% at 12 courses, and 47% at more than 12 courses. Nevertheless, two allergic reactions were found at the first course; one of these was mild, while the other was an anaphylactic reaction. When an adverse reaction occurs, the dilemma of whether to continue therapy arises. We administered a further infusion of carboplatin in patients presenting grade 1 and 2 allergic reactions; only in approximately 30% of the cases was premedication able to prevent an allergic reaction.

In conclusion, hypersensitivity is negligible if carboplatin is administered for a small number of courses, whereas it is impressive (47%) for a higher number of courses (more than 12). Therefore, we suggest that the risk of hypersensitivity should be considered in the protocols using repeated administration of carboplatin.

REFERENCES

1. Morgan JS, Adams M, Mason MD. Hypersensitivity reactions to carboplatin given to patients with relapsed ovarian carcinoma. Eur J Cancer 1994;30:1205–1206.
2. Wiesenfeld M, Reinders E, Corder M, et al. Successful retreatment with cis-dichlorodiammine platinum after apparent allergic reactions. Cancer Treat Rep 1979;63:219–221.
3. Planner RS, Weerasiri T, Timmins D, et al. Hypersensitivity reactions to carboplatin. J Natl Cancer Inst 1991;83:1763–1764.
4. Shlebak AA, Clark PI, Green JA. Hypersensitivity and cross-reactivity to cisplatin and analogues. Cancer Chemother Pharmacol 1995;35:349–351.
5. Tonkin KS, Rubin P, Levin L. Carboplatin hypersensitivity: case reports and review of the literature. Eur J Cancer 1993;29:1356–1357.
6. Weidmann B, Mülleneisen N, Bojko P, et al. Hypersensitivity reactions to carboplatin. Cancer 1994;73:2218–2222.
7. Sood AK, Gelder MS, Huang SW, et al. Anaphylaxis to carboplatin following multiple previous uncomplicated courses. Gynecol Oncol 1995;57:131–132.
8. Windom HH, McGuire WP, Hamilton RG, et al. Anaphylaxis to carboplatin-A new platinum chemotherapeutic agent. J Allergy Clin Immunol 1992;90:681–683.
9. Saunders MP, Denton CP, O'Brien MER, et al. Hypersensitivity reactions to cisplatin and carboplatin-a report on six cases. Ann Oncol 1992;3:574–576.
10. Hendrick AM, Simmons D, Cantwell BMJ. Allergic reactions to carboplatin. Ann Oncol 1992;3:239–240.
11. Bacha DM, Caparros-Sison B, Allen JA, et al. Phase I study of carboplatin (CBDCA) in children with cancer. Cancer Treat Rep 1986;70:865–869.
12. Gaynon PS, Ettinger LJ, Moel D, et al. Pediatric phase I trial of carboplatin: a Children's Cancer Study Group report. Cancer Treat Rep 1987;71:1039–1042.
13. Chang SM, Fryberger S, Crouse V, et al. Carboplatin hypersensitivity in children: a report of five patients with brain tumors. Cancer 1995;75:1171–1175.
14. Allen JC, Walker R, Luks E, et al. Carboplatin and recurrent childhood brain tumors. J Clin Oncol 1987;5:459–463.
15. Packer RJ, Lange B, Ater J, et al. Carboplatin and vincristine for recurrent and newly diagnosed low-grade gliomas of childhood. J Clin Oncol 1993;11:850–856.