
Carboplatin desensitization

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Background: IgE-mediated carboplatin hypersensitivity reactions occur in up to 30% of patients receiving this agent for chemotherapy of solid tumors, thus limiting therapeutic options.

Objective: To describe our experience with intravenous carboplatin desensitization regimens, which culminated in a standardized, successful protocol for safe administration.

Methods: Eight consecutive patients with ovarian cancer who had experienced severe anaphylactic reactions to carboplatin were referred to our hospital. Intradermal skin testing was performed by raising a 3-mm bleb by injection of undiluted carboplatin at 10 mg/mL, and the wheal size was read at 20 minutes. The outcomes of the various desensitization regimens were documented prospectively, and the experience gained was used to develop a standardized protocol for administration.

Results: All patients had positive intradermal skin test results. The first 3 patients were treated with short (90 minutes to 6 hours) desensitization protocols, and all protocols failed on the first or second infusions. These 3 and a subsequent 5 patients were given intravenous carboplatin according to a protocol of gradual dose escalation over a 4-log dose range given during a 4-day period, with subsequent 3-weekly infusions given more rapidly by omitting the most dilute log dose on each occasion. All patients tolerated the longer infusion protocol without event, and all but 1 patient experienced appropriate tumor marker response.

Conclusions: Short carboplatin desensitization protocols (less than 6 hours) have an unacceptable failure rate in patients with carboplatin allergy, but longer infusion times (days) are well tolerated without recurrence of the allergic reaction and with good tumor response. In cases where carboplatin is the optimal therapeutic agent, clinicians should not be deterred by an anaphylactic reaction to it or by failure of shorter desensitization regimens.

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INTRODUCTION

Carboplatin is an important drug for a variety of adult and pediatric malignancies, particularly advanced ovarian cancer. The fact that it causes no nephrotoxic effects, neurotoxic effects, or severe nausea has made it the preferred drug over its parent compound, cis-platinum. The use of carboplatin is limited by the development of systemic allergic reactions in up to 30% of these patients.¹ Onset of carboplatin-induced hypersensitivity typically occurs after multiple cycles of carboplatin, most commonly during the eighth cycle, which typically corresponds to the second dose of reinduction therapy following tumor relapse.² Thus, the prevalence of carboplatin allergy increases to 44% when restricted to patients receiving a second course.³ These reactions can include flushing, nausea, diarrhea, abdominal pain, bronchospasm, urticaria, hypotension, and death and typically occur when approximately 50% of the drug has been infused.⁴ Symptoms usually develop within the first 30 minutes of an infusion but rarely may occur up to several days afterward. Such hypersensitivity reactions occur despite premedication with dexamethasone and antihistamines, which are usually given routinely. The reason for the high incidence of allergy to carboplatin is unclear, although the risk is particularly increased after the fifth dose and when the drug is administered weekly.⁵ No obvious risk factors are apparent that might

allow the identification of those who might experience severe reactions as opposed to mild symptoms.² The reactions are believed to be IgE mediated based on compatible clinical features and positive skin test results.

Affected patients must either avoid the drug completely, with suboptimal therapeutic alternatives, or undergo desensitization. Three approaches to desensitization have been reported in the literature: lasting 90 minutes,⁶ 6 hours,⁷ and a period of days.⁸ Our initial experience with adaptations of the 2 shorter protocols was disappointing and prompted us to develop an approach using a slow infusion over days, with subsequent shortening of the infusion time with each chemotherapy cycle. Herein, we describe our experience with intravenous carboplatin desensitization regimens and detail a standardized, successful protocol for safe administration.

METHODS

Eight consecutive patients with ovarian cancer and a history of carboplatin allergy, referred to the Immunology Service, Westmead Hospital, Westmead, Sydney, Australia, were reviewed clinically and underwent skin testing. Intradermal skin testing was performed by raising a 3-mm bleb by injection of undiluted carboplatin at 10 mg/mL, and the wheal size was read at 20 minutes. The outcomes of the various desensitization regimens were documented prospectively, and the experience gained was used to develop a standardized protocol for administration.

RESULTS

The first 3 patients referred for carboplatin desensitization were initially managed by attempting the shorter protocols described

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Table 1. Patient Characteristics

Patient No.	Initial reaction	Infusion No. of reaction	Intradermal skin test result	Dose, mg	2-Hour protocol	6-Hour protocol	4-Day protocol	CA125 response, U/mL
1 (First desensitization course)	Hypotension, chest tightness, abdominal pain, urticaria	8	24 × 165 mm	400	Failed on first attempt	Not attempted?	First over 4 days, second over 3 days, third over 3 days	120–16
2	Hypotension, nausea, and urticaria	8	5 × 5 mm	545	Not attempted	First tolerated, second reaction	First over 4 days, second over 3 days, third and fourth over 2 days	214–17.7
3	Blurred vision, generalized numbness, fever, bronchospasm, neck angioedema	9	5 × 4 mm	600	Not attempted	First tolerated, second reaction	First, second, and third over 4 days, treatment suspended, fourth, fifth and sixth over 4 days, seventh over 3 days, eighth over 2 days, ninth over 1 day	436–44 300–70
1 (Second desensitization course)	Not applicable	Not applicable	Negative at baseline, 30 × 20 mm after first infusion	555	Not attempted	Not attempted	First over 2 days, second over 4 days, third over 3 days, fourth over 2 days, fifth and sixth over 1 day	57–24
4	Urticaria, cough, dyspnea	8	7 × 6 mm	770	Not attempted	Not attempted	First over 4 days, second over 3 days, third over 2 days, fourth over 1 day	68–10
5	Hypotension, syncope, nausea, diaphoresis	8	15 × 10 mm	550	Not attempted	Not attempted	First over 4 days, second over 3 days, third over 2 days, fourth and fifth over 1 day	388–10
6	Hypotension, syncope, erythroderma	8	13 × 11 mm	650	Not attempted	Not attempted	First over 4 days, second over 3 days, third over 2 days, fourth and fifth over 1 day	25–13
7	Felt hot, abdominal pain with vomiting and diarrhea, paresthesia	8	9 × 8 mm	600	Not attempted	Not attempted	First over 4 days, second over 3 days, third over 2 days, fourth over 1 day	158–95
8	Urticaria	8	5 × 5 mm	450	Not attempted	Not attempted	First over 4 days	230–no response

in the literature.^{6,7} The failure of these protocols in all 3 patients, with recurrent symptoms of systemic allergic reactions, prompted the subsequent development of a protocol for slow infusion with escalation of dose rate on each subsequent cycle and is outlined in the following 3 cases (Table 1).

Patient 1

A 64-year-old woman with stage IIIC ovarian cancer was treated with debulking surgery followed by 5 monthly cycles

of carboplatin and paclitaxel. On the fifth cycle, she developed fever, dyspnea, flushing, and tachycardia, which did not recur after omitting paclitaxel from the sixth cycle. The tumor relapsed 2 years later, and single-agent carboplatin was given. Ten minutes into the second cycle, she experienced an allergic reaction manifest by hypotension, chest tightness, abdominal pain, and urticaria (Table 1). The result of an intradermal skin test to carboplatin (10 mg/mL) performed 1 month later

was positive. A 2-hour desensitization protocol (Table 2) was unsuccessful despite antihistamine and steroid premedication, with the development of ear pain, nausea, abdominal cramping, diarrhea, flushing, and hypotension during the second log dose; all symptoms responded to hydrocortisone and ranitidine. This prompted us to devise a 4-day desensitization protocol in which the infusion rate increased gradually over a 4-log dilution range (Table 3). This was tolerated without event. Two subsequent infusions were given during 3 days by omitting the most dilute log dose (Table 3), again without event, and with appropriate CA125 response. One year later, she re-presented with recurrence of ovarian cancer, and intradermal skin test results to carboplatin had become negative. A 2-day infusion was tolerated, but given the natural history of the development of carboplatin allergy, namely, sensitization and anaphylaxis during additional courses of the drug, we repeated the skin testing before her next carboplatin cycle, the results of which became positive. The cycle was therefore given for 4 days, with subsequent infusions again shortened by 1 day by omitting the most dilute log dose until a 2-day infusion was achieved (Table 3). All 3 subsequent cycles proceeded uneventfully.

Patient 2

A 72-year-old woman with ovarian cancer received initial treatment with surgery followed by 6 cycles of carboplatin and paclitaxel. Following relapse 3 years later, an additional course of carboplatin was given, and an allergic reaction occurred on the second infusion, manifest by hypotension, nausea, and urticaria (Table 1). A further 12 cycles of paclitaxel failed to achieve remission, with rising CA125 levels, and she was referred to our hospital. Intradermal skin test results to carboplatin were positive. Given the experience of the first patient, the 2-hour infusion was bypassed in favor of the 6-hour infusion (Table 4), but nevertheless she reacted on the second 6-hour infusion, with ear pain and urticaria developing during the third log dose, and responded to hydrocortisone and loratadine. The 4-day protocol (Table 3) was tolerated without problems, and again the most dilute log

Table 2. Two-Hour Protocol for Desensitization to Carboplatin*

Time, min	Carboplatin (of total dose)
0-30	1/1,000
30-60	1/100
60-90	1/10
90-120	Remainder

* Data are from Zanotti et al.⁶ The total dose of carboplatin was diluted in 150-mL bags of isotonic sodium chloride solution each of which was infused over a 30-minute period. All patients were given premedication with dexamethasone, 20 mg orally at night, for 3 nights before infusion; loratadine, 10 mg orally in the morning, on day of infusion; then dexamethasone, 20 mg orally or intravenously, and ranitidine, 100 mg intravenously, 30 minutes before infusion. Dexamethasone, 10 mg orally, and loratadine, 10 mg orally, were continued for 2 days after each course.

Table 3. Four-Day Protocol for Desensitization to Carboplatin*

Time, h	Carboplatin (of total dose, in 1,000-mL bags)	Rate, mL/h	% of total dose infused
Day 1			
0	1/1,000	10	0.003
3	1/1,000	14	0.0042
6	1/1,000	20	0.006
9	1/1,000	28	0.0084
12	1/1,000	38	0.0114
15	1/1,000	50	0.015
18	1/1,000	75	0.0225
21	1/1,000	100	0.03
Day 2			
0	1/100	10	0.03
3	1/100	14	0.042
6	1/100	20	0.06
9	1/100	28	0.084
12	1/100	38	0.114
15	1/100	50	0.15
18	1/100	75	0.225
21	1/100	100	0.3
Day 3			
0	1/10	10	0.3
3	1/10	14	0.42
6	1/10	20	0.60
9	1/10	28	0.84
12	1/10	38	1.14
15	1/10	50	1.5
18	1/10	75	2.25
21	1/10	100	3.0
Day 4			
0	Remainder	10	2.67
3	Remainder	14	3.7
6	Remainder	20	5.3
9	Remainder	28	7.5
12	Remainder	38	10.1
15	Remainder	50	13.3
18	Remainder	75	20
21	Remainder	100	26.7

* The total dose of carboplatin was diluted in 1-L bags of isotonic sodium chloride solution, each of which was infused over a 24-hour period, with logarithmic escalation in the infusion rate every 3 hours as shown. In most patients (Table 1), the most dilute bag was omitted from subsequent cycles, reducing the total infusion time by 1 day, until a single day's infusion was achieved. All patients were given premedication with dexamethasone, 20 mg orally at night, for 3 nights before infusion. During the infusions, patients received oral loratadine, 10 mg daily, dexamethasone, 20 mg daily, and ranitidine, 150 mg twice daily. Dexamethasone, 10 mg orally, and loratadine, 10 mg orally, were continued for 3 days after each course. In some patients who developed delayed minor allergic symptoms during the days following the infusion, loratadine was continued for a week.

dose was omitted with each subsequent infusion until a 2-day infusion was achieved. All infusions were tolerated without event, and the CA125 level decreased appropriately.

Patient 3

A 62-year-old woman with stage IV ovarian cancer was treated with surgery and 6 cycles of carboplatin given monthly. Following relapse 2 years later, a course of carbo-

Table 4. Six-Hour Protocol for Desensitization to Carboplatin*

Time, h	Carboplatin (of total dose, in 250-mL bags)	Rate, mL/h	Total dose infused, %
0	1/1,000	60	0.012
0.5	1/1,000	140	0.028
1	1/1,000	300	0.06
1.5	1/100	60	0.12
2	1/100	140	0.28
2.5	1/100	300	0.6
3	1/10	60	1.2
3.5	1/10	140	2.8
4	1/10	300	6
4.5	Remainder	60	10.7
5	Remainder	140	24.9
5.5	Remainder	300	53

* Data are from Windom et al.⁷ The total dose of carboplatin was diluted in 250-mL bags of isotonic sodium chloride solution, each of which was infused over a 90-minute period, with logarithmic escalation of the rate of infusion every 30 minutes as shown. All patients were given premedication with dexamethasone, 20 mg orally at night, for 3 nights before infusion; loratidine, 10 mg orally in the morning, on day of infusion; then dexamethasone, 20 mg orally or intravenously, and ranitidine, 100 mg intravenously, 30 minutes before infusion. Dexamethasone, 10 mg orally, and loratidine, 10 mg orally, were continued for 2 days after each course.

platin was commenced. On the third cycle, she developed a generalized allergic reaction manifest by blurred vision, generalized numbness, fever, bronchospasm, and neck angioedema (Table 1); hence, her treatment was continued with paclitaxel alone. This regimen failed to control her disease, and she was referred to our hospital. Intradermal skin test results to carboplatin were positive. She tolerated the first 6-hour protocol well but reacted to the second, with palm itching, abdominal cramping, chest tightness, and dyspnea during the third log dose, which responded to hydrocortisone and subcutaneous adrenaline. She therefore began the 4-day desensitization regimen (Table 3), and a further 2 infusions proceeded without event. There was an appropriate CA125 response, and her treatment was suspended. However, after a further increase in CA125 level, she received another 6 carboplatin cycles, the first 3 of these given during 4 days and the remainder during 3, 2, and finally just 1 day without reaction and again with good tumor marker response (Table 1).

Based on this experience, a protocol was adopted for all patients with a history of a systemic allergic reaction to carboplatin with a positive intradermal test result. The total carboplatin dose was given as an inpatient in a progressively increasing intravenous infusion regimen for 4 days under antihistamine and steroid cover (Table 3). Infusions were given every 3 weeks, and on each occasion the most dilute log dose was omitted, making each infusion 1 day shorter than the preceding one. A further 5 patients were treated using this approach, all with advanced inoperable ovarian cancer, elevated CA125 levels, and positive skin test results

to carboplatin (Table 1). There were no allergic reactions from any of the desensitization infusions, and all patients tolerated treatment well. Most were able to achieve a single-day infusion. The CA125 levels decreased to normal levels in all but 1 of these patients, who only received a single infusion and whose disease was thought to be resistant to platinum agents.

DISCUSSION

We have carefully documented the development of a protocol to enable carboplatin to be given to patients with advanced ovarian cancer who are allergic to it. This approach differs from previously reported ones in that it uses a slowly increasing dose escalation during a 4-day period and gradual shortening of this infusion time with each subsequent infusion. This approach met with no failures in the 8 patients treated to date.

There have been a small number of case series reporting the use of 90-minute to 6-hour desensitization protocols in patients with carboplatin hypersensitivity, but the success rate of these shorter regimens seems limited. Windom et al⁷ described a single patient who tolerated repeated 4-hour desensitization infusions. Zanotti et al⁶ used a 90-minute protocol for patients who became skin test positive during a course of carboplatin, and of 5 patients so treated, 3 subsequently reacted. Goldberg et al⁸ described 2 patients in whom desensitization failed using a 4-hour protocol, both of whom underwent successful desensitization using longer regimens, 1 for more than 15.5 hours and the other for more than 81.5 hours. Robinson et al⁹ treated 4 carboplatin-allergic patients with an intravenous protocol of a duration between 4 and 8 hours, none of whom reacted. Longer regimens seem to be better tolerated, with Rose et al⁴ reporting greater success with a protocol in which the first 3 log dilutions were given for more than 90 minutes each and the last 1 for more than 12 hours, making a total infusion time of 16.5 hours. Of the 33 patients thus treated, most tolerated it well, although 4 reacted during initial administration and a further 3 during subsequent doses, representing a failure rate of 21%. In the first 3 of our patients, shorter infusion times (2 or 6 hours) failed; however, these patients tolerated a regimen significantly longer than that used by Rose et al,⁴ but this regimen became shorter on each infusion and had no failures, notwithstanding the significant drawback of a hospital stay for several days.

Slowly increasing dose escalation during desensitization is a common practice in allergy; however, most previous reports of carboplatin desensitization have used a constant infusion rate for each log dose level, often resulting in a 10-fold increase in administration rate at each step. We reasoned that this rapid increase in dose rate was possibly too sudden for these exquisitely allergic patients and was also unnecessary, since a smoother increase in drug exposure can easily be achieved by meticulously pursuing a more gradual quasi-exponential increase within each log dose level (Table 3). Further research would be required to determine whether using this strategy during a single 24-hour period might decrease the failure rate of the 16.5-hour infusion reported by Rose et al⁴ and

also reduce the need for prolonged hospital admission, although reports of fatalities justify some caution.¹⁰

Slow infusion of carboplatin into a patient who is allergic is clearly achievable based on the current report and those of others, but 2 further observations suggest that doing so results in allergen-specific tolerance and therefore constitutes true desensitization. First, we were able to reduce the duration of infusion from 4 days to 1 day without precipitating an allergic reaction, suggesting increasing drug tolerability over time. We have not proven, of course, that allergic patients were intolerant of a 24-hour infusion in the first instance, although their prompt reactions during the shortened 90-minute or 6-hour infusions and the failure rate reported by Rose et al⁴ might suggest that this was likely to be the case. Second, the one patient in whom the skin testing was repeated showed reversion to skin test result negativity following a successful course of 6 desensitization infusions. That she resensitized on subsequent repeated exposure suggests that the propensity of the individual to mount an allergic reaction is not influenced by desensitization and that ongoing intermittent exposure to the drug is necessary to maintain the tolerant state. This seems to contrast with desensitization to other drugs, which requires continuous exposure to maintain this tolerance. We speculate that the latency interval between intermittent drug exposures in the case of carboplatin extends for 2 to 3 weeks and allows the administration of this agent more rapidly with each infusion, but to prove this an initial intolerance to a 24-hour infusion would need to be demonstrated.

Intradermal skin testing with undiluted carboplatin performed before each infusion in nonallergic patients has been shown by Zanotti et al⁶ to have a good negative predictive value (99%). In that study, the development of a positive test result during a course of carboplatin was also predictive of a subsequent allergic reaction, occurring in 6 of 13 patients, 3 reacting during a 90-minute desensitization protocol undertaken based on the positive skin test result alone.⁶ In our hands, skin testing at least seemed very sensitive in that all 8 of our clinically allergic patients had a positive skin test result and no results were false negative, although we did not test a control population.

The slow infusion rate used here might have risked diminishing carboplatin's antitumor effects. However, this appeared not to be the case, since 7 of the 8 patients studied showed a tumor marker response completely consistent with normal administration of this drug, and the last patient received only a single infusion and may well have been platinum resistant. The preserved efficacy of a slow infusion might have been predicted, since our protocol resulted in almost 90% of the total drug dose being administered in the final 24-hour period, and the antitumor effects of carboplatin have been shown to be proportional to the area under the curve rather than the peak serum concentration.⁸

We have demonstrated the success of a carboplatin desensitization protocol that involves a slow increase in the rate of administration involving a 4-log dilution range and given

over a 4-day period under steroid and antihistamine cover, with subsequent 3-weekly infusions given by omitting the most dilute log dose until a single day infusion is achieved. Shorter protocols (over hours) showed predictable failure in our experience and cannot be endorsed, since administering carboplatin to those allergic to it is a potentially serious situation in which deaths have been reported.¹⁰ However, we believe that longer regimens, as reported herein, can be given safely and successfully and that clinicians should not refrain from giving carboplatin to patients who are allergic to it or in whom short desensitization regimens fail.

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