Hypersensitivity following Retreatment with Carboplatin a Decade after Completion of Primary Platinum-Based Chemotherapy

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Key Words

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Abstract

The relatively rapid development of a platinum-associated hypersensitivity reaction in an ovarian cancer patient receiving second-line chemotherapy more than a decade following her last course of primary platinum-based chemotherapy demonstrates that the prolonged persistence of immune cells recognizing platinum after sensitization has been established.

Introduction

The development of platinum hypersensitivity reactions is a well-recognized and potentially serious problem in cancer management [1–6]. The large majority of platinum-associated allergies are observed following multiple (>5–6) cycles of treatment, and in the case of ovarian cancer, such reactions are most frequently seen when this class of agents is delivered in the second-line setting [3]. Overall, as many as 10–15% of ovarian cancer patients treated with carboplatin for recurrent disease will experience this complication of the treatment program.

It has been hypothesized that the usual prolonged delay in development of platinum hypersensitivity in susceptible individuals results from extremely low concentrations of metallic platinum that may be a nonmeasurable contaminant during the process of

preparing the clinically utilized platinum agents (cisplatin, carboplatin, oxaliplatin) [3]. In fact, clinically relevant allergic reactions to platinum itself are a well-recognized occupational hazard for platinum miners [7–9].

While the period of greatest risk for observing hypersensitivity has been described, limited information is available regarding what is actually occurring during this period of sensitization when a susceptible patient continues to receive the drug without experiencing allergic symptoms. Further, assuming a patient has become sensitized but does not receive further platinum for an extended period of time, will reintroduction of a platinum agent quickly result in a reaction, or will another extended period of sensitization be required?

The development of a major allergic reaction to reintroduction of carboplatin in an ovarian cancer patient with recurrent disease who had not received any chemotherapy for more than a decade provides one provocative answer to this question.

Case Report

The patient, a 23-year-old female, was initially diagnosed as having a stage 3C papillary serous ovarian cancer of low malignant potential in February 1996. A second surgery performed later that same year confirmed the presence of an extensive tumor with this histology.

Following treatment with 6 cycles of carboplatin plus paclitaxel in early 1997, the patient remained without evidence of disease until August 2008, when during the performance of a laparoscopic cholecystectomy an abdominal wall mass was noted that revealed a grade 1 papillary serous adenocarcinoma. In September 2008, an exploratory laparotomy documented multiple intra-abdominal and peritoneal nodules with pathology confirming a low-grade papillary serous adenocarcinoma.

The patient was started on a regimen of carboplatin plus paclitaxel. (Note: This carboplatin regimen was reinitiated more than 10 years following the completion of her last course of platinum-based chemotherapy.)

The first 2 cycles were tolerated well, but within 3–5 min of initiating the carboplatin infusion during cycle 3, the patient began to sneeze and cough, subsequently developing facial flushing with itching and watery eyes. Her blood pressure and pulse remained stable. The patient was observed for 30 min, at which time the infusion was restarted. She again developed sneezing. Within 15 min of the completion of the infusion the patient experienced progressive erythema, flushing of her face, neck, abdomen and arms, as well as diffuse itching. She was treated with fluids, corticosteroids and diphenhydramine, with gradual improvement in her symptoms. However, facial flushing persisted for several days.

Following discussions regarding possible treatment options and considering the fact that the patient had had an extended treatment-free interval, she had therapy continued with a cisplatin and weekly paclitaxel program. As of the time of preparation of this report, several cycles of this modified platinum regimen have been delivered without the development of a hypersensitivity reaction.

Discussion

The clinical course and symptoms observed in this patient are classical for platinum hypersensitivity [3]. Accumulated experience would suggest that the first cycle following the reintroduction of a platinum agent apparently serves to provide a substantial boost in stimulating the proliferation or biological activity of specific immune cells in a patient previously sensitized, such that when the next few cycles are administered, the signs and symptoms of full-blown allergy result. In fact, one report noted that cycle 8 or 9 of platinum (i.e., the second or third course after resuming this class of agents following the initial 6 cycles of the primary platinum-based chemotherapy) are the most frequent cycles where such reactions are observed [3].

However, what is unique about this case is the extended period (>10 years) between the last course (cycle 6 of the primary regimen) and the resumption of a platinum agent (carboplatin) delivered in the second-line setting. This experience provides strong support for the conclusion, even if currently based solely on an individual case report, that if a patient becomes sensitized to platinum the responsible immune cells will persist for very prolonged periods of time and are capable of rapid expansion or activation resulting in an allergic reaction following retreatment with this class of cytotoxic agents [10].

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