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Carboplatin Hypersensitivity: Case Reports and Review of the Literature

Katia S. Tonkin, Peter Rubin and Leslie Levin

INTRODUCTION

CHEMOTHERAPY FOR carcinoma of the ovary is usually based on a platinum agent. Historically, cisplatin has been considered the most active agent in ovarian cancer and there have been numerous trials comparing cisplatin with carboplatin. These trials have tended to show that there is therapeutic equivalency between the two drugs and since carboplatin is less nephrotoxic and less emetogenic than cisplatin, it has in some centres become the drug of choice for first-line treatment.

We report here two cases of hypersensitivity reactions to carboplatin. In both cases the reaction occurred on third challenge with carboplatin which we anticipate will be seen more frequently when patients are treated with carboplatin as first-line treatment.

CASE STUDIES

Case 1

A 64-year-old lady presented with a stage III, grade 1 serous papillary carcinoma of the ovary in March 1988. The patient received two cycles of cyclophosphamide and cisplatin. She suffered hypomagnesaemia, hypokalaemia and an increase in her serum creatinine to 120 mg/ml and, therefore, on the third course of treatment carboplatin was substituted for cisplatin.

She received a total of six cycles of chemotherapy and remained in clinical remission for 2 years. At that time, recurrent disease was treated with four cycles of carboplatin alone. After approximately 8 months there was again radiological evidence of recurrence in the abdomen. In November 1991, she began salvage chemotherapy with single-agent carboplatin. On the third course the patient was halfway through her chemotherapy when she developed tightness around her throat, felt flushed and developed generalised erythema. She was afebrile. There was no change in pulse or blood pressure. Examination of the chest was unremarkable.

She was treated with benadryl, solucortef and prednisone. All symptoms resolved within 1 h and the rash disappeared within 2 h.

Case 2

A 68-year-old woman presented in 1986 with a stage III poorly differentiated papillary adenocarcinoma of the ovary. She received six cycles of carboplatin and cyclophosphamide; second-look laparotomy confirmed she was pathologically free of disease. She remained well until 1990 and then relapsed in the abdomen. At that time, she had completed seven cycles of single agent carboplatin and was well until May 1991. She developed recurrence in the abdomen and was recommenced on carboplatin. During the third cycle she developed erythema, chest pain and shortness of breath. Initially, on examination, she had a few wheezes in the left upper zone posteriorly, but there was no change in pulse or blood pressure. She was treated with intravenous (i.v.) cogentin, epinephrine mg, 1/1000 i.v. and was subsequently given stemetil 10 mg i.v. for vomiting. She was then treated with hydrocortisone 100 mg i.v. All symptoms and signs resolved within 1 h. She was admited overnight, but did not require any further treatment.

DISCUSSION

Both these patients had received a third challenge of carboplatin. In the case of the first patient, initial treatment had been started 3 years prior to the third challenge and in the second patient, treatment had started 5 years earlier.

Both these patients developed a widespread erythamatous rash and both noticed chest pain as part of the reaction.

A number of chemotherapy agents are known to cause hypersensitivity reactions. *Escherichia coli* L-asparaginase is responsible for the highest prevalence of hypersensitivity reactions and cisplatin is the second with a frequency of approximately 20% [1]. It would appear that the prevalence of these reactions appears to increase when a number of chemotherapy agents are used in combination. The spectrum of symptoms reported are similar to the patients in this report. It is established that complex salts of platinum are highly allergenic in industry where a number of workers have reported immediate hypersensitivity reactions and allergic asthma [2].

The mechanism of the cisplatin-mediated allergic response has been studied by several groups. Typical type I skin, nasal and bronchial reactions were elicited with solutions of platinum halide complex salts in a group of refinery workers suggesting that IgE mast cell interaction was taking place [3]. In another case [4], a type II allergic response occurred, despite the fact that antibodies could not be demonstrated by serological tests. The particular property of the platinum complex that produces allergy could not be elucidated, but it has been suggested that cisplatin binds to serum proteins to act as a hapten.

Carboplatin appears to have a similar spectrum of activity as its parent compound. The dose-limiting toxicity of this agent is myelosuppression, rather than neuro- or nephrotoxicity which probably relates to structural differences between the two drugs [5].

In a recent study, Kawano *et al.* [6] were unable to elicit systemic or cutaneous anaphylaxis in guinea-pigs using carboplatin emulsified with freunds complete adjuvant. This suggests the immunogeneity of this compound is in part related to the host or perhaps, as in our patients, the number of previous exposures or time from first exposure. Planners *et al.* [7] have also observed anaphylactic reactions in 2 patients receiving carboplatin. In both cases these patients were heavily pretreated with cisplatin-containing regimens.

In view of the nature of these reactions, we feel that further carboplatin is contraindicated in these patients.

Correspondence to K. Tonkin at 790 Commissioners Road E., London, Ontario, Canada N6A 4L6.
P. Rubin and L. Levin are at the Department of Medical Oncology, London Regional Cancer Centre, London, Ontario, Canada.
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Meningeal Tumour Infiltration in Hormone Resistant Prostate Cancer Demonstrated with Magnetic Resonance

Viggo Blomlie, Gustav Lehne, Hans H. Lien, Mette Winderen and Sophie D. Fosså

PALLIATION OF symptoms is the main goal of treatment in hormone resistant prostate cancer. Neurological disturbances may present as paraplegia, general cerebral dysfunction or cranial nerve palsy. The latter is frequently due to extension of skull base metastases to neighbouring neural structures [1, 2]. Cerebral dysfunction and cranial neuropathy may also be due to metastases to the meninges as we have observed in 6 patients in our hospital. Such lesions may be demonstrated with gadolinium dimeglumine (Gd-DTPA) enhanced magnetic resonance (MR) imaging.

A 59-year-old patient with adenocarcinoma of the prostate underwent MR because of impaired vision of the left eye. Contrast enhanced MR images demonstrated diffuse meningeal metastases on the left side with a large tumour in the temporal region adjacent to the optic nerve (Fig. 1). The vision improved considerably following 3 days of radiotherapy combined with high dose dexamethasone (4 mg × 4 daily) per os. The patient died of his widespread malignancy 5 months later.

The acute or subacute development of cerebral dysfunction or cranial nerve palsy in an elderly man is no rare event and is often interpreted as a sign of cerebrovascular infarction. In a patient with prostate cancer such symptoms should raise the suspicion of an intracranial tumour manifestation. The present case illustrates that meningeal metastasis may be the cause of the symptoms.

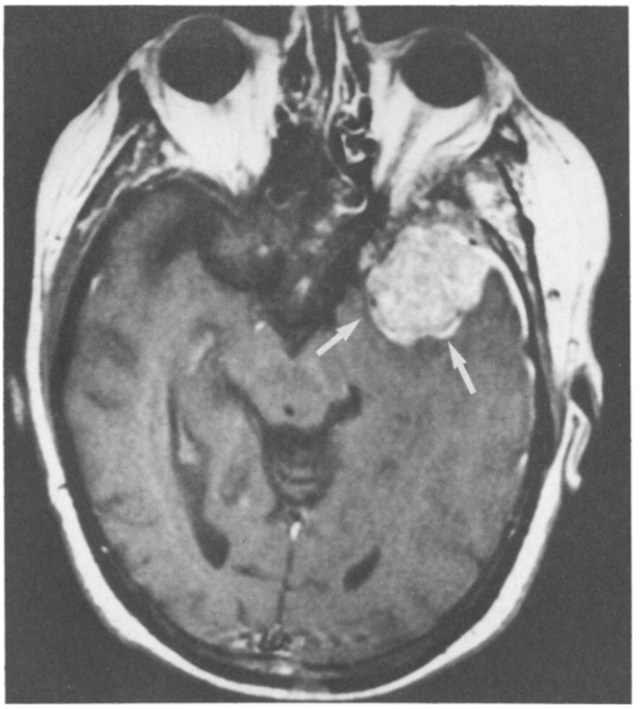

Fig. 1. Bulky meningeal metastasis in left temporal region demonstrated with contrast enhanced MR (arrows).

Involvement of the meninges has previously been demonstrated with contrast enhanced MR imaging in carcinomas of the breast, lung, oesophagus, head and neck and lymphoma and leukaemia [3]. Most of these have shown diffuse curvilinear enhancement underneath the inner table of the skull or small nodular tumours on the surface of the brain [3, 4]. A bulky metastasis like in the present patient seems unusual.

There is evidence that the incidence of meningeal metastases is particularly high in cancer patients with longtime survival. CT and radionuclide bone scan may be negative in spite of widespread meningeal involvement.

The palliative treatment of meningeal tumour in patients with hormone resistant prostate cancer consists of radiotherapy and high dose dexamethasone and may result in a dramatic relief of symptoms. Though the median survival is only 8 months, the effectiveness of such treatment with regard to improving quality of life justifies the cost of a contrast enhanced MR examination to make a correct diagnosis.

Correspondence to V. Blomlie.
The authors are at the Norwegian Radium Hospital, Montebello, N-0310 Oslo, Norway.
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