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SHORT COMMUNICATION

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Hypersensitivity and cross-reactivity to cisplatin and analogues

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Abstract We report on a 49-year-old woman with relapsing ovarian cancer who developed a hypersensitivity reaction (HSR) to carboplatin and, subsequently, to cisplatin. This patient was known to be allergic to Co-Amoxiclav and talc, both giving rise to a transient macular skin rash, but had no other history of atopy. Similar cases, including some of life-threatening severity, have been reported in the literature. These severe reactions may prevent a small population of young patients from receiving effective therapy with cisplatin or its analogues, treatment known to be associated with a significant improvement in survival in germ-cell tumours, ovarian cancer and osteogenic sarcoma.

Key words Hypersensitivity · Cross-reactivity · Cisplatin Analogues

Introduction

Cisplatin and its analogues are the most active agents in potentially curable germ-cell tumours [3] and osteogenic sarcoma, as well as being effective agents in ovarian cancer, where they are associated with significant survival benefit. The use of these drugs is associated with very well recognised and predictable toxic effects, including nausea, vomiting, nephrotoxicity and neurotoxicity. With the exception of neurotoxicity, the other toxic effects are largely preventable by the use of currently available anti-emetics and adequate hydration.

Hypersensitivity reactions with a wide spectrum of clinical severity ranging from asymptomatic rashes to severe anaphylaxis have been seen in approximately 5% of reported series [21]. Platinum salts were first noticed to produce bronchial asthma as an occupational hazard among platinum-refinery workers in 1945 [13]. With their introduction to clinical practice as anticancer agents, an association with type I hypersensitivity reactions (HSRs) was subsequently confirmed [9]. Severe HSRs to these agents, though rare, may be life-threatening and their occurrence is unpredictable.

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Case report

A 49-year-old woman with relapsing ovarian cancer developed HSRs manifesting as vomiting, tightness of the chest and anaphylaxis requiring resuscitation with oxygen, intravenous hydrocortisone and antihistamines. No adrenaline was required since the reaction could be reversed with the above measures. Other recognised manifestations seen were anxiety, pruritis, cough, dyspnoea, sweating, vomiting, bronchospasm and hypotension. The timing of the two episodes relative to disease progression and treatment are shown in Table 1; both occurred within the first few minutes of commencement of the third cycle, 2 and 4 years, respectively, after the patient's first exposure to cisplatin. Dexamethasone was used as an anti-emetic on both occasions.

Table 1 Summary of the history of the present patient

June 1987	Moderately differentiated stage III left ovarian adenocarcinoma was diagnosed, treated with oophorectomy and post-operative pelvic radiotherapy.
May 1989	First relapse with right ovarian adenocarcinoma treated with TAH, right salpingo-oophorectomy and infra-colic omentectomy followed by four cycles of adjuvant chemotherapy (cisplatin + cyclophosphamide).
December 1991	Second relapse with retroperitoneal lympadenopathy and right-sided hydronephrosis with mild to moderate renal impairment, treated with carboplatin; an anaphylactic reaction developed on cycle 3, after which chemotherapy was discontinued. CT scan showed partial remission.
February 1992	Treatment with oral chlorambucil for 5 cycles, completed July 1992.
November 1993	Third relapse with right hydronephrosis and stable, mild renal impairment, re-treated with single-agent cisplatin, then development of a further anaphylactic reaction, again occurring at the third cycle.

Table 2 Summary of reported cases of HSR

Reference	Platinum analogue	Number of patients (%)	HSR type	Route of administration
[5]	Cisplatin	5/24 1/24	Mild type I Severe type I	Intravesical
[11]	Cisplatin	7/67 (10)	Type I	Intravesical
[2, 4]	Cross-reactivity: cisplatin and carboplatin	2	Type I	Intravenous
[7]	Carboplatin	1	Type I	Intravenous
[6, 10]	Iproplatin	2	Type I	Intravenous
[14, 19]	DACCP	(6.6) (15)	Type I Type I	Intravenous Intravenous

Discussion

HSRs are very well recognised with administration of cisplatin and its analogues via different routes, with the intravesical route being more commonly implicated as compared with intravenous or intraperitoneal administration [5, 11]. Systemic absorption from the intravesical, intravenous and intraperitoneal routes is recognised, and there is no clear reason to explain the increased frequency associated with intravesical administration [18]. Table 2 shows that many of the reported cases of HSR require repeated exposure to such agents, as was the case with our patient.

Other platinum analogues such as iproplatin and DACCP are known to be associated with similar HSRs, and the latter seems to have a higher incidence of such reactions. Cross-reactivity has been reported in three cases [2, 4], whereas in other cases analogues used to treat patients who have reacted to cisplatin have been used safely with no cross-reactivity [10].

The mechanism of hypersensitivity has been studied in only a few patients; whereas Khan et al. [15] have demonstrated an IgE-mediated process, other investigators have failed to confirm this [22]. Skin-test reactivity to the drug has been reported [20]. Type II HSRs with haemolytic anaemia have been reported in small numbers of patients [8, 12, 17], with a causal relationship to cisplatin administration being proven by direct anti-globulin test and recurrence of the haemolysis on re-challenge with the drug. Zeger et al. [23] have shown that cisplatin can cause non-immune binding to red cells and immunoglobulins, giving a false-positive direct anti-globulin test finding even in the absence of haemolysis. Other concomitant medications, including mannitol, have rarely been incriminated [1, 16], underlining the importance of a comprehensive drug history.

The Clatterbridge Centre for Oncology treats over 200 new patients annually with platinum-containing regimens for ovarian cancer, germ-cell tumours and osteogenic sarcomas, and anaphylactic reactions have not been seen since the administration of chemotherapy was centralised in 1 unit 7 years ago. However, the regular use of dexamethasone as an anti-emetic may partially explain the low incidence of these HSRs.

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