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Magnetic Resonance Signal Alterations of the Brain in Asymptomatic Patients Treated With High-dose Cisplatin for Ovarian Carcinoma

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THE FEATURES of high-dose cisplatin-induced neurotoxicity have been described as transient acute cerebral dysfunction and chronic leucoencephalopathies [1,2].

We incidentally observed the presence of high-signal intensity lesions on T2 weighted images located in periventricular white matter in a patient under cisplatin chemotherapy treatment for ovarian carcinoma. The patient was neurologically asymptomatic.

This finding induced us to perform brain magnetic resonance (MR) on another 19 patients who were also under cisplatin treatment for ovarian carcinoma. All the patients were symptom-free and cisplatin dose was 120 mg/m^2 as a 4-h infusion in each cycle, administered over 3–5 days.

MR examinations were performed on the fifth day of treatment with a 0.2 T unit (Hitachi). Axial and saggital TI (500/30), PD and axial T2 weighted (1900/30–90) sequences were obtained. Intravenous GdTPA was administered in the axial TI sequence.

Of the 20 patients, 10 showed abnormalities of white cerebral matter, presenting as high signal intensity focal lesions on T2 weighted images. The lesions were well defined, with irregular margins, and were located preferentially in periventricular white matter. Intravenous GdTPA showed no signal changes. There was no ventricular dilatation or other cerebral abnormality in any case.

These lesions may be related to multiple foci of non-inflammatory leucoencephalopathy secondary to cisplatin adminstration, microclots or necrotising embolisms of tumoral tissues [3,4], although we were not able to obtain histological correlation.

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The Use of Carboplatin in Malignant Germ Cell Tumours

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CARBOPLATIN HAS been used in trials for patients with good risk germ cell tumours in order to avoid cisplatin-associated treatment toxicity [1]. In a phase II trial recently published in

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Table 1. Antitumour activity of cisplatin (DDP) and carboplatin (CDDP) in four heterotransplanted human testicular cancer cell lines (2102 EP, H 12.1, 1428 A and H 23.1)

	Dose	Relative tumour volume at day 30			
		2102 EP	H 12.1	1428A	H 23.1
DDP	3 mg/kg days 1–5 i.p.	0.23	0.22	0.21	2.0
CDDP	12.5 mg/kg days 1–5 i.p	1.2	1.7	1.9	2.1
Control	—	2.9	3.5	4.9	3.8

i.p., intraperitoneally. Values are given for the relative tumour volume at the end of the experiment (day 30) in comparison to untreated control animals.

the *European Journal of Cancer* 24 patients with good risk (according to IGR criteria) non-seminomatous germ cell cancer were treated with four cycles of carboplatin and etoposide (CE regimen) [2]. With adverse events, such as tumour progression, viable tumour at surgical resection or relapse occurring in 37.5% of the patients, the authors concluded that the CE regimen used was inferior to standard cisplatin-based therapy. In their excellent discussion the authors mention that this result may be related to the dosing of carboplatin, which was based on body surface area and not the area under the curve as calculated from creatinin clearance by the Calvert formula [3]. Furthermore, the low dose intensity of etoposide may have contributed to this result since only a total dose of 360 mg/m^2 of etoposide was applied in 28-day intervals.

As only mentioned briefly in the discussion, one further explanation for the results obtained in the above-cited trial may be that the antitumour activity of carboplatin is truly inferior to cisplatin. Early preclinical investigations of our group have compared the *in vivo* antitumour activity of equitoxic doses (LD 20) of carboplatin and cisplatin in xenografts from four human testicular cancer cell lines transplanted in nude mice [4]. This *in vivo* model had been successfully established to evaluate the effects of new cytostatic agents [5]. In three of four cell lines tested a dose of 12.5 mg/kg × 5 days of carboplatin was significantly less active than 3 mg/kg × 5 days of cisplatin, with respect to the reduction of the mean relative volume of the heterotransplanted tumours in nude mice. In the fourth cell line (H 23.1), known to be cisplatin-resistant, neither carboplatin nor cisplatin achieved a significant reduction of tumour volume in comparison with untreated controls (Table 1). If the results obtained in nude mice experiments can be applied to the clinics, a dose of 450 mg/m^2 of carboplatin may only be equivalent to no more than 45 mg/m^2 of cisplatin. Similar results, indicating inferior antitumour activity of carboplatin in comparison to cisplatin in a xenograft tumour model, have also been reported in ovarian cancer cell lines [6].

Three cycles of the PEB regimen (cisplatin/etoposide/bleomycin) remain the treatment of choice for patients with good risk testicular cancer. If carboplatin is substituted for cisplatin, this must be compensated for by the addition of a third active agent, e.g. bleomycin given at full dose, in combination with full doses of etoposide, as proposed by Horwich and colleagues using a CEB regimen (carboplatin/etoposide/bleomycin) [7]. In a phase II study, the CEB combination has achieved a 2-year event-free survival of 93.3%. However, the results of a randomised comparison of the CEB regimen to standard cisplatin combination chemotherapy are still awaited.

In patients with relapsed testicular cancer the relative absence of non-haematological toxicity of carboplatin allows dose escalations of this agent not achievable with cisplatin. Combination regimens containing ultra high dose carboplatin (1500–2400 mg/m^2) followed by autologous bone marrow support have already been successfully used in phase II studies [8]. Therefore, carboplatin may possibly gain a role in the high dose treatment of patients with relapsed disease rather than in reducing toxicity in the treatment of patients with good risk testicular cancer.

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