Table 1. Response to chemotherapy and survival of all patients

Response	No. of patients (%)	Primary tumours	Duration of response, weeks (median)	Overall survival, weeks (median)
CR	1 (4.54)	SCLC	32	31–88 (46.28)
PR	6 (27.27)	3 SCLC 3 NSCLC	22–31 (25.33)	
NC	3 (13.63)	1 breast 1 NSCLC 1 occult	10–20 (16.33)	10–44 (26.0)
P	11 (50.0)	5 NSCLC 1 SCLC 2 breast 1 uterus 2 occult		2–66 (24.63)
NE	1 (4.54)	breast		

CR, complete remission; PR, partial remission; NC, no change; P, progression; NE, not evaluable.

cancer) who had had previous treatment with one or more different types of chemotherapy. 3 of these patients (2 NSCLC, 1 SCLC) had had previous treatment with platinum derivatives. All the patients under study had cerebral metastases documented by contrast-enhanced brain computed tomography (CT), carried out after the beginning of steroid therapy. All the patients were treated with carboplatin (300 mg/m^2 day 1 every 4 weeks) associated with etoposide (120 mg/m^2 days 1–3 every 4 weeks). Clinical evaluation was carried out before every cycle of chemotherapy, while CT scan was practiced every two cycles. Response to therapy and toxicity were valued in accordance with WHO criteria; overall survival was calculated in weeks from the date of the beginning of chemotherapy. The patients eligible for evaluation were 21 as 1 patient (breast cancer) refused to continue therapy after the first course. Altogether 64 cycles of chemotherapy were administered. Response to chemotherapy, duration of response and survival of all patients are shown in Table 1. Of the 7 patients who responded to treatment, 3 partial response (PR) had had previous chemotherapy: 2 of these (1 NSCLC, 1 SCLC) with platinum derivatives. In 6 cases, the site of progression was the encephalus, sometimes associated with extracranial disease. In 1 case, cutaneous metastases continued development.

Toxicity did not cause delays or reduction of doses. In 3 patients, who had showed WHO grade IV myelotoxicity, treatment was, however, suspended because of progression.

Our data show how the replacement of cisplatin with carboplatin, which is less toxic and certainly more manageable, maintains the same high level of success as the etoposide–cisplatin combination. The best results have, therefore, occurred in the treatment of the tumours which are most sensitive to the combination. In the treatment of brain metastases from lung cancer, the association of carboplatin and etoposide could be a valid alternative to traditional radiotherapy. In fact, as we know, the brain is rarely the sole site of metastases [2], and patients receiving cranial irradiation alone almost always die of extracranial tumour rather than cerebral metastases, therefore a chemotherapy treatment will be necessary.

The chemotherapy, when it is efficacious, can be useful for controlling all the sites of metastases including cerebral lesions. This may be particularly useful when using well tolerated drugs like carboplatin and etoposide.

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European Journal of Cancer Vol. 30A, No. 8 pp. 1205–1206, 1994.

0959–8049/94 $7.00 + 0.00

Hypersensitivity Reactions to Carboplatin Given to Patients With Relapsed Ovarian Carcinoma

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ALTHOUGH HYPERSENSITIVITY reactions to cisplatin occur in 1–20% of patients [1], hypersensitivity reactions to carboplatin appear uncommon, occurring in less than 8% of patients [2–5].

We have reviewed the case notes of 180 cases of histologically proven overian carcinoma treated with single-agent intravenous carboplatin at the Velindre Hospital. Overall, 8.7% of patients developed a hypersensitivity reaction. However, of 34 patients given a second and third course of carboplatin on relapse, 15 (44%) developed a hypersensitivity reaction compared to only one reaction seen in 180 patients during their first course of carboplatin ($P<0.01$, Fisher's exact test).

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Revised 10 Nov. 1993; accepted 19 Jan. 1994.

Table 1. Cumulative risk of a hypersensitivity reaction with cycle number of carboplatin

Cycle no.	No. of patients receiving cycle	No. of patients with hypersensitivity	Cumulative risk of hypersensitivity (%)
6	34	2	6
7	32	8	25
8	24	13	54
9	20	12	60
10	12	8	67

No difference in total dose, total dose per metre squared or overall time from first exposure to carboplatin was seen during repeated courses of carboplatin between those patients developing and not developing a hypersensitivity reaction.

However, the cumulative risk of a reaction increased from 6% (2 out of 34) at cycle six to 67% (8 out of 12) by cycle 10 of carboplatin (Table 1) ($P<0.01$, χ^2 test). This high incidence compares well to the occupational setting, where repeated exposure to platinum salts can cause hypersensitivity reactions in 60% of people [6]. The low incidence of hypersensitivity reactions to carboplatin in oncological settings is mainly derived from studies using carboplatin either as a first-line agent or following cisplatin at relapse [3–5].

In 14 patients with hypersensitivity reactions, further carboplatin was given safely. In 10/11 patients, prophylactic chlorpheniramine [10 mg i.v. (intravenous) prior to carboplatin and 4 mg orally three times daily for 24 h postinfusion] prevented further hypersensitivity reactions. This is similar to the experience with cisplatin [7], and suggests further carboplatin can be safely given following hypersensitivity reactions with prophylactic chlorpheniramine. However, we did not attempt further platinum therapy in the 1 patient with anaphylactic shock.

The mechanism of hypersensitivity reactions to carboplatin is unclear. The prolonged period of sensitisation and rapid onset of symptons during carboplatin infusions would support a role for a type I IgE-mediated mechanism. In the occupational setting, there is good evidence to support this mechanism for platinum salt hypersensitivity [8, 9]. However, in the treatment setting, other mechanisms may operate, such as non-immunological histamine release, as suggested by the absence of evidence for IgE type I hypersensitivity in two cases of cisplatin hypersensitivity [7].

Whatever the mechanism, hypersensitivity reactions to carboplatin appear to be increasingly common with repeated prolonged use, and easily avoidable with chlorpheniramine. This permits the continued use of carboplatin in patients where mild or moderate hypersensitivity symptoms have occurred.

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European Journal of Cancer Vol. 30A, No. 8, pp. 1206–1207, 1994.

0959-8049/94 $7.00 + 0.00

0959-8049(94)E0101-9

Phase II Study of Mitomycin C Plus 5-fluorouracil in Patients with Refractory Ovarian Cancer

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PATIENTS WITH advanced ovarian cancer refractory to cisplatin-containing combinations have an extremely unfavourable prognosis [1]. One of the highest response rates obtained in this group of patients was reported by Alberts and colleagues who used a combination of mitomycin C and 5-fluorouracil (5-FU) in patients with advanced disease refractory to cisplatin with a 40% remission rate [2]. These impressive results prompted us to start a phase II study to confirm these data.

Eligibility criteria were pathological proof of epithelial ovarian cancer, prior platinum chemotherapy, measurable disease, no central nervous system metastases, performance status (WHO)$\leq$ 2, leucocytes $\geq$ 3500/mm^3, platelets $\geq$ 100 000/mm^3 and serum creatinine $\leq$ 1.2 mg/dl. Informed consent was obtained in all cases. Patients were treated as follows: mitomycin C 10 mg/m^2 intravenously (i.v.) on day 1 every 6 weeks and 5-FU 500 mg/m^2 i.v. on days 1 to 3 every 3 weeks. Routine laboratory analysis and CA-125 were performed on days 1 and 21 of each course. Response on therapy was assessed after two courses and WHO criteria were followed to evaluate both response and toxicity.

From October 1990 to December 1992, 18 consecutive patients entered this study, 15 of them being fully evaluable, 2 only for response (because of rapid progression and death) and 1 for toxicity (insufficient treatment due to grade 3 diarrhoea).

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Revised 10 Jan. 1994; accepted 24 Jan. 1994.