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A COMPARISON OF THE TOXICITY AND EFFICACY OF CISPLATIN AND CARBOPLATIN IN ADVANCED OVARIAN CANCER

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Abstract

Eighty-eight patients with stage IIB–III epithelial ovarian cancer were randomised to receive first line single agent cisplatin (100 mg/m^2) monthly or carboplatin (400 mg/m^2) monthly for up to 5 cycles. Crossover to the opposite analogue occurred with progression or lack of response. All patients were premedicated with i.v. methylprednisolone (500 mg at 0 hours and 250 mg at 3 hours) and the first 20 patients in both groups received lorazepam and prochloperazine for nausea and vomiting. The median number of vomiting episodes per cycle with cisplatin was 16 and with carboplatin 2 ($p<0.001$). In the cisplatin arm 27/40 (67.5%) developed mild renal toxicity, 9/40 (22.5%) WHO grade I neurotoxicity and 18/40 (45%) evidence of ototoxicity at audiometry. To date we have seen no neuro- or ototoxicity with carboplatin and 1/40 (2.5%) have developed WHO grade I renal toxicity. Myelosuppression and anaemia was more common with carboplatin but only 1 episode of grade IV thrombocytopenia has been seen with first line carboplatin. The clinical response rate (CR+PR) for cisplatin was 19/40 and for carboplatin 27/40. Actuarial survival for cisplatin group at 24 months was 50% and for carboplatin group 58% with no significant difference. Carboplatin appears less toxic than cisplatin producing to date similar survival and response as a single agent.

Key words: Ovarian cancer; cisplatin, carboplatin, toxicity, efficacy, randomized study.

Cisplatin is the most active drug in ovarian cancer whether used alone or in combination (1, 2) but toxicity may be severe. Neuropathy and nephropathy is dose limiting and cisplatin-induced nausea and vomiting may greatly impair quality of survival. The platinum analogue carboplatin (JM8) has been suggested to be significantly less toxic than cisplatin with similar efficacy (3) and consequently a possible alternative to cisplatin in ovarian cancer. In 1984 a controlled trial in patients with advanced ovarian cancer was set up in South Wales to further define the relative toxicities and efficacies of these drugs and preliminary data is reported. Single agent platinum regimens were used since it has not yet been proven that the addition of other drugs, e.g. doxorubicin improves survival (4) whilst they may significantly increase toxicity.

Material and Methods

Only patients with histologically verified FIGO stage IIB, III or IV, epithelial ovarian cancer were included. All patients had residual macroscopic tumour after primary surgery. Patients were excluded if they had received primary chemotherapy or radiotherapy, were older than 70 years, had a creatinine clearance of less than 60 ml/min, a Karnofsky performance status of less than 60, or had inadequate marrow reserve (leukocyte count less than 3 500/μl or a platelet count less than 150 000/μl) (see Table 1 for patient characteristics).

Within 4 weeks of primary laparotomy eligible patients were randomly assigned to receive single agent cisplatin or carboplatin monthly.

Cisplatin was administered in a dose of 100 mg/m^2 i.v. over 6 h after 24 h of pre-hydration (3 l), and mannitol diuresis followed by a further fluid (3 l post-hydration).

Crossover to the opposite analogue occurred with progression, failure to respond after 4 cycles or when they had clinically residual tumour after 5 cycles. Patients clinically disease-free after 5 treatment cycles proceeded to surgical restaging preferably assessed with a laparotomy, peritoneal cytology and multiple biopsies at sites of previous disease. Where laparoscopy was employed for surgical restaging, biopsies of sites of previous disease

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Table 1

Characteristics of patients according to treatment

Characteristics	Carboplatin n (%)	Cisplatin n (%)
Eligible for study	40	40
Mean age (years)	58	56
Mean Karnofsky performance index	88	84
FIGO stage		
IIB	1 (2.5)	3 (7.5)
III	30 (75)	27 (67.5)
IV	9 (22.5)	10 (25)
Residual tumour before chemotherapy		
<2 cm	3 (7.5)	5 (12.5)
2.5 cm	15 (37.5)	12 (30)
>5 cm	22 (55)	23 (57.5)

and peritoneal cytology was always carried out. Patients histologically clear of tumour (negative biopsies and peritoneal cytology) continued with a further 5 cycles of the same platinum analogue at a reduced dose, 30 mg/m^2 for cisplatin and 300 mg/m^2 for carboplatin depending on toxicity. Patients with residual tumour crossed over to the opposite analogue.

Toxicity was defined by WHO criteria and in all patients serial serum creatinine, liver function tests, creatinine clearance, EDTA clerance and audiometry was carried out. The severity of nausea and vomiting was recorded for all treatment cycles by recording the number of vomiting episodes, the duration of vomiting and the duration of delayed nausea and anorexia (for anti-emetic policy see Table 2).

Results

Eighty-eight patients have been randomised and 80 patients have been evaluated for first-line response and toxicity analysis (crossover data is at present incomplete).

Nausea and vomiting. All patients were pre-medicated with i.v. methylprednisolone and the first 15 cisplatin and carboplatin patients received lorazepam and prochloperazine as required (Table 2 A). With this regimen, the severity of nausea and vomiting with cisplatin was significantly more severe than with carboplatin (Table 3). The median number of vomiting episodes per cycle with cisplatin was 16 versus with carboplatin 2 ($p<0.0001$). The median duration of vomiting per cycle with cisplatin was 12 h versus with carboplatin 1 h ($p<0.0001$). The median duration of delayed nausea with cisplatin was 3 days versus with carboplatin 0 days ($p<0.0001$). The median duration of anorexia with cisplatin was 3 days versus with carboplatin 0 days ($p<0.0001$). All p-values were determined with the Mann-Whitney U-test.

Since nausea and vomiting was severe with 'as required' lorazepam and prochloperazine, the subsequent 10 cisplatin patients were pre-medicated with lorazepam and prochloperazine (anti-emetic regimen B, Table 2). This resulted in a significant reduction in the number of vomiting episodes after cisplatin ($p<0.02$) but the vomiting remained severe with a median of 12 episodes (Table 3) with no significant reduction of the duration of the vomiting or delayed nausea or anorexia.

Since nausea and vomiting with cisplatin remained unacceptably severe high dose i.v. metoclopramide with subsequent cisplatin patients was administered maintaining methylprednisolone pre-medication (Table 2 C).

The use of high dose metoclopramide significantly reduced the number of vomiting episodes with cisplatin

Table 2

Anti-emetic regimens

A	
Methylprednisolone	500 mg i.v. 0 h, 250 mg i.v. 3 h
Prochloperazine	12.5 mg i.m. as required q 4 h
Lorazepam	1–2 mg orally bd
B	
Methylprednisolone	500 mg i.v. 0 h, 250 mg i.v. 3 h
Prochloperazine	25 mg rectally q 4 h pre-medication
Lorazepam	1–2 mg orally bd
C	
Methylprednisolone	500 mg i.v. 0 h, 250 mg i.v. 3 h
Metoclopramide	60 mg i.v. 0, 3, 6, 9 h

Table 3

Nausea and vomiting according to therapy

Treatment	No. of patients	Anti-emetic regimen		
A. *No. of vomiting episodes treatment cycle*			Median number	
Cisplatin	15	A	16	p<0.0001
Carboplatin	20	A	2	
Cisplatin	10	B	12	
Cisplatin	15	C	4	p<0.01
Carboplatin	20	B	2	
B. *Duration of vomiting*			Duration (hours)	
Cisplatin	15	A	12	p<0.0001
Carboplatin	20	A	1	
C. *Duration of delayed nausea*			Median duration (days)	
Cisplatin	15	A	3	p<0.0001
Carboplatin	20	A	0	
Cisplatin	15	C	3	p<0.0001
Carboplatin	20	B	0	
D. *Duration of delayed anorexia*			Median duration (days)	
Cisplatin	15	A	3	p<0.0001
Carboplatin	20	A	0	
Cisplatin	15	C	3	p<0.0001
Carboplatin	20	B	0	

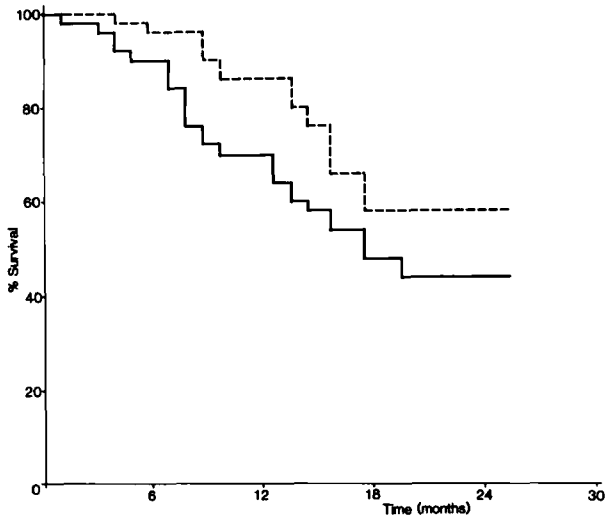

Fig. 1. Actuarial survival. Carboplatin: --- (n=40). Cisplatin: —— (n=40).

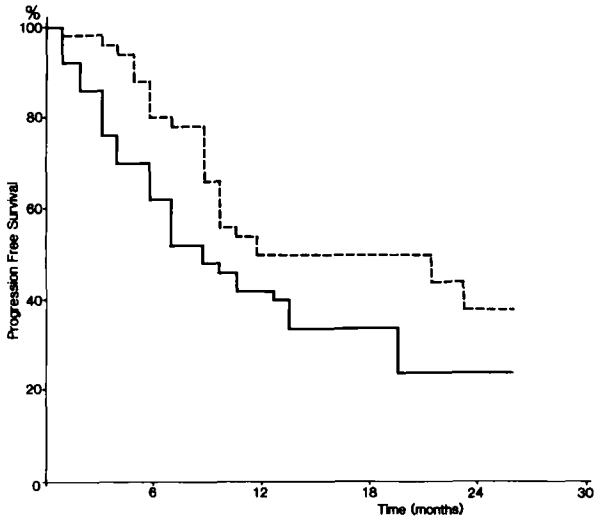

Fig. 2. Actuarial progression-free survival. Carboplatin: --- (n=40). Cisplatin: —— (n=40).

Table 4

Toxicities according to first line drug therapy

Toxicity	WHO grade	Carboplatin n (%)	Cisplatin n (%)
Neurotoxicity	0	0	31 (77.5)
	1	0	9 (22.5)
	2–4	0	0 (0)
Ototoxicity (audiometry)		0	18 (45)
Nephrotoxicity*	Nil	39 (97.5)	13 (32.5)
	Mild	1 (2.5)	26 (65)
	Moderate	0	1 (2.5)
	Severe	0	0
Fall in creatinine clearance (40%)		0	14 (35)
Myelosuppression			
Hb<9.5 g		11 (27.5)	5 (12.5)
WBC	0–1	34 (85)	38 (95)
	2	5 (12.5)	2 (5)
	3	1 (2.5)	0
	4	0	0
Platelets	0	27 (67.5)	40 (100)
	1	6 (15)	0
	2	3 (7.5)	0
	3	3 (7.5)	0
	4	1 (2.5)	0
Alopecia	0	39 (97.5)	39 (97.5)
	1	1 (2.5)	1 (2.5)
	2–4	0	0

* Mild = serum creatinine exceeds 1.26–2.5 × pre-treatment level
moderate = serum creatinine exceeds 2.6–5 × pre-treatment level
severe = serum creatinine exceeds 5–10 × pre-treatment level.

Table 5

Response to platinum therapy

Response	Carboplatin n (%)	Cisplatin n (%)
Pathological complete response (L)*	7	4
Pathological complete response (P)*	1 (20)	2 (15)
Microscopic disease	3 (7.5)	1 (2.5)
Partial response	16 (40)	12 (3.0)
No response	13 (32.5)	21 (52.5)

* (L)=laparotomy, (P)=laparoscopy.

(median=4) but this still remains significantly greater than carboplatin (n<0.01), and this had no effect on the duration of delayed nausea and anorexia with cisplatin (median of 3 days) versus carboplatin (median 0 days). Thus the severity of nausea and vomiting for every parameter measured was more severe with cisplatin than carboplatin irrespective of anti-emetic regimen.

Other toxicities (Table 4). Neurotoxicity has not been seen with carboplatin but has occurred in 22.5% of cisplatin patients. Similarly ototoxicity has not occurred with carboplatin but has occurred in 45% of cisplatin patients, as measured by audiometry (30 decibel hearing loss between 4000 and 8000 Hz). Nephrotoxicity has been rare with carboplatin occurring in only 1 patient compared to 67% of cisplatin patients as determined by the defined criteria (Table 4) and 35% of cisplatin patients had a fall in creatinine clearance greater than 40%. Myelosuppression in both treatment arms has been mild, being more common with carboplatin. Haemoglobin fell to less than 9.5 g in 27.5% of carboplatin patients compared to 12.5% of cisplatin patients. Grade IV leukopenia was not seen in either treatment arms and grade I leukopenia was seen in only 1 carboplatin patient. Significant thrombocytopenia did not occur in the cisplatin arm and was present in 32.5% of carboplatin patients. One patient had grade IV thrombocytopenia with normal renal function but had a

low baseline platelet count of 167000/μl. Minimal alopecia was rare in both treatment arms.

Efficacy. More partial and pathological responses have been seen with carboplatin than cisplatin but the difference is not statistically significant (Table 5). Actuarial survival at 24 months (Fig. 1) is similar as is progression-free survival (Fig. 2) and there is no statistically significant difference. Preliminary data suggests similar efficacy for both of these drugs.

Conclusion

Carboplatin appears to be significantly less toxic than cisplatin. Whilst thrombocytopenia with carboplatin is dose limiting, in this study in patients with adequate renal function and bone marrow reserve myelosuppression was not severe and data suggests that there is scope for increasing the dose. In addition carboplatin with its ease of administration and its reduced emetic effect is amenable to out-patient therapy. Whilst high dose metoclopramide combined with steroids may significantly reduce the severity of immediate cisplatin vomiting, it has no effect on delayed nausea and anorexia which is a distressing morbidity in these patients. It does not require hydration or intensive anti-emetic regimens, needed for cisplatin. The efficacy of these 2 drugs appears to be similar according to preliminary data. Therefore until more aggressive cytotoxic therapy or more novel approaches are proved to have definite survival advantages in advanced ovarian cancer, carboplatin is a very acceptable treatment option offering sigificantly better quality of life for these patients.

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