Eur J Cancer Clin Oncol, Vol. 24, No. 9, pp. 1471–1479, 1988.
Printed in Great Britain

0277-5379/88$3.00 + 0.00

Comparative Toxicity of Cisplatin, Carboplatin (CBDCA) and Iproplatin (CHIP) in Combination with Cyclophosphamide in Patients with Advanced Epithelial Ovarian Cancer

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Abstract—*Sixty patients with FIGO stage IIb, IIc, III and IV ovarian cancer were entered into a randomized Phase III study of cyclophosphamide* 600 mg/m^2 *with cisplatin* 100 mg/m^2, *iproplatin* 240 mg/m^2 *or carboplatin* 300 mg/m^2. *Dose modifications were made according to renal function and myelotoxicity. The arms containing carboplatin (CBDCA) and iproplatin (CHIP) were not shown to be significantly different from the cisplatin containing arm with regard to response rate, duration of response and survival.*

Subjective toxicity showed that cisplatin and cyclophosphamide therapy was associated with more nausea and vomiting ($P = 0.0005$). *The duration of vomiting showed a significant increase with successive courses of chemotherapy for the cisplatin containing arm only* ($P < 0.003$). *The cyclophosphamide/CHIP combination caused significantly more diarrhoea* ($P < 0.0006$). *Alopecia was more severe* ($P < 0.02$), *and neurotoxicity was more common, in patients who received cyclophosphamide and cisplatin (paraesthesiae* $P = 0.0007$, *tinnitus* $P < 0.00005$, *deafness* $P = 0.0018$).

All three combinations caused cumulative toxicity on haemoglobin (Hb) ($P < 0.001$ *for each treatment), leukocyte count (WCC)* ($P < 0.0005$ *for each treatment), and platelet count* ($P < 0.0005$ *for each treatment). The degree of fall in Hb for each course of therapy was greater in the cisplatin containing arm compared with the CHIP and CBDCA arms which were not significantly different from each other* ($P = 0.0005$). *For WCC the cisplatin/cyclophosphamide regimen was significantly less toxic than CHIP/cyclophosphamide, with CBDCA/cyclophosphamide falling between the two and not being significantly different from either* ($P = 0.0005$). *The CHIP containing arm caused more thrombocytopenia than the other arms which were of equal toxicity* ($P < 0.0005$).

Serum creatinine showed a gradual significant overall rise with each course of cisplatin/cyclophosphamide therapy ($P < 0.0005$), *whereas the CBDCA arm showed no change and the CHIP arm showed a small fall in serum creatinine after most courses of therapy.*

This study showed that CHIP or CBDCA in combination with cyclophosphamide was less toxic than cisplatin/cyclophosphamide therapy with regard to alopecia, degree and duration of nausea and vomiting, renal toxicity, neurotoxicity and anaemia. The CHIP/cyclophosphamide regimen caused more thrombocytopenia and diarrhoea. The CHIP and CBDCA containing arms caused more leukopenia than the cisplatin containing regimen. Either iproplatin or carboplatin would be an acceptable alternative to cisplatin in chemotherapy regimens, and would result in reduced toxicity.

INTRODUCTION

ALKYLATING AGENTS have been extensively used to treat metastatic ovarian cancer, with response rates ranging from 35 to 65% [1]. Randomized trials comparing alkylating agents to non-cisplatin containing chemotherapy regimens have generally shown superior response rates for the combination with improved remission duration [2–9]. A smaller number of studies have shown inferior or equivalent response rates [10–12]. However, only two of these

Accepted 28 April 1988.
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studies have shown improved survival for patients treated with combination chemotherapy [7, 8].

Cisplatin has been shown to be active as a single agent in the treatment of epithelial ovarian cancer, with a response rate of more than 50% in previously untreated patients [13]. Randomized trials of combination chemotherapy with one arm containing a cisplatin regimen have shown a higher complete response rate for the cisplatin containing arm [14–19], with improved survival reported in three studies [14, 17, 19].

A recent retrospective analysis of chemotherapy for ovarian cancer showed a distinct advantage for multiagent regimens over single alkylating agent therapy in terms of survival, and the advantage was especially marked for cisplatin containing regimens [20].

Combination chemotherapy regimens and cisplatin therapy have been criticised for toxicity when survival benefit is likely to be small. Cisplatin causes dose related nephrotoxicity, neurotoxicity, myelotoxicity, high tone deafness and protracted emesis [21]. Platinum analogues have been manufactured with the aim of reducing toxicity.

Cis-dichloro-*trans*-dihydroxy-bis-isopropylamine platinum IV (iproplatin or CHIP) has been assessed in Phase I and II studies and shown to have activity in patients with ovarian cancer, and less toxicity than cisplatin [22, 23].

Phase I studies of *cis*-diammine-1,1-cyclobutane dicarboxylate platinum II (carboplatin—CBDCA) have shown a lack of renal and ototoxicity [24, 25]. A phase II study has shown activity in ovarian carcinoma [26].

As cisplatin containing regimens are associated with a high complete remission rate, we have evaluated the toxicity of cisplatin and the two analogues iproplatin and carboplatin in combination with cyclophosphamide in a three arm, randomized study, in patients with epithelial ovarian cancer. The dosage of iproplatin used was 240 mg/m^2 and that of carboplatin was 300 mg/m^2, both being derived from phase I/II studies [23–25].

This paper reports the results of this randomized study, with emphasis on toxicity.

PATIENTS AND METHODS

Criteria for eligibility

Patients aged ≤65 years, with a Karnofsky performance ≥60% [27], and a histologically proven diagnosis of epithelial ovarian carcinoma were eligible for entry into the study. The pathology was reviewed in all cases, and the following subtypes were acceptable, serous or mucinous cyst-adenocarcinoma, endometroid carcinoma, clear cell carcinoma and undifferentiated carcinoma. Patients with FIGO stage IIb, IIc (post-operative residual), III and IV were eligible for entry into the study. At randomization, patients were stratified for histological grade and amount of post-operative residual disease (>2 cm defined as bulk).

Previously untreated patients were entered into the study, if investigations before therapy showed that the leukocyte count was $>3.5 \times 10^9$/l, platelets $>150 \times 10^9$/l, serum creatinine <0.15 mmol/l, and creatinine clearance was >50 ml/min. Patients with serious concurrent medical illness were excluded from the study.

Chemotherapy regimens

All patients received cyclophosphamide at a dose of 600 mg/m^2. Patients were randomized to receive cisplatin 100 mg/m^2, iproplatin 240 mg/m^2 or carboplatin 300 mg/m^2.

The cyclophosphamide was dissolved in 500 ml 0.9% saline and infused over 1 h. The platinum analogue was then given in 1 l of intravenous fluid. Following this *only* patients randomized to cisplatin received post-therapy hydration with 3 l of 0.9% saline over 18 h.

Six cycles of therapy were given at 4 weekly intervals if the WCC $> 3.0 \times 10^9$/l, and the platelet count was $>100 \times 10^9$/l at the time chemotherapy was due.

Antiemetic therapy

All patients received the same antiemetic regimen—100 mg metoclopramide before chemotherapy as a 1 h infusion. In addition lorazepam 4 mg was given intravenously before therapy. Patients then received metoclopramide 20 mg parenterally every 4 h for five doses. Patients were discharged with a supply of metoclopramide tablets and prochloroperazine suppositories. The amount used was documented at the next visit, together with an account of the duration and severity of emesis or nausea.

Antidiarrhoeals

Codeine phosphate 60 mg was given to all patients before therapy, and 6 h after the onset of treatment. The occurrence of diarrhoea in hospital or at home was documented.

Pretreatment and follow-up investigations

Before randomization the full medical history and clinical examination were documented, along with the Karnofsky perfomance (KP) status. Blood was taken for a full blood count, urea and electrolytes, serum creatinine, serum calcium and magnesium, biochemical profile and liver function tests. The creatinine clearance was measured. Chest radiographs and CT scans of the abdomen and pelvis were routinely performed. Patients well enough to travel also had audiograms (Amploid 300 audiometer), and caloric function tests [28] at the audiology clinic (Manchester Royal Infirmary).

Patients were seen weekly after the first course of chemotherapy, and 2 weekly after subsequent courses. The KP was recorded and toxicity documented according to WHO criteria [29]. The above blood tests and creatinine clearance tests were repeated at each visit. A full clinical examination, including pelvic examination, was performed monthly in addition to the above tests.

After therapy was completed patients who did not have clinical evidence of progressive disease had a repeat CT scan, chest radiograph and audiogram.

Dose modifications

Dosage reduction of the platinum analogue *only* was according to nadir blood counts. A reduction of 25% was made if the nadir platelet count was $50–74 \times 10^9$/l. A 50% reduction was made if the WCC nadir was $<0.9 \times 10^9$/l, or the platelet nadir $<49 \times 10^9$/l. Delays in therapy of up to 2 weeks were allowed if the leukocyte count was $<3.0 \times 10^9$/l or the platelet count $<100 \times 10^9$/l when the next course was due, or if the creatinine clearance was <50 ml/min. If the creatinine clearance was 30–50 ml/min after 2 weeks delay 50% of the platinum analogue was given, but if it was <30 ml/min patients were withdrawn from the study.

Second look laparotomies

These were performed if patients had not had a bilateral salpingo-oophorectomy and hysterectomy (BSOH) before therapy, or if post therapy CT scans suggested the presence of residual tumour that could be removed surgically. Laparotomy was not carried out routinely in patients who had achieved an apparent complete remission following BSOH and chemotherapy.

Follow up

After completion of therapy patients were reviewed every 2 months for the first year, 3 monthly during the second and third years, 6 monthly up to 5 years, then annually.

Definitions of response and toxicity

The criteria for response and grades of toxicity were according to those defined by the World Health Organization [29]. The CT scans were reviewed by two people (JMcG and HA). Patients who had normal CT scans before and after therapy were classed as minimal residual disease and were unevaluable for response unless a second look laparotomy showed a pathological complete remission, or disease progression occurred. Patients with abnormal CT scans showing measurable tumour before therapy, that were assessed as normal after therapy were classified as having obtained a clinical complete remission. Freedom from progression and survival have been calculated from the date of starting chemotherapy.

Statistical methods

Pre-treatment values of haemoglobin (Hb), leukocyte count (WCC), platelet count, and serum creatinine were compared for each treatment group using the Kruskal–Wallis (K–W) non-parametric one way analysis of variance [30]. The detection of any change in these values over time was analysed for individuals within each treatment group using Friedman's non-parametric two way analysis of variance [30]. If the Friedman test was statistically significant then the way values changed with time for each treatment group was analysed for significance using multiple Wilcoxon match pairs signed rank tests, with a reduced significance level of $P < 0.001$ for each test. The K–W non-parametric one way analysis of variance was used to compare all the values over time for each treatment group. If this detected a significant difference then multiple Mann–Whitney (M–W) U tests using a reduced significance level of 0.017 were applied to see which pairs of groups were different. Linear regression (LR) analysis was used to determine overall trends for toxicity of each treatment group (i.e. looking for cumulative toxicity) by testing the significance of the slope of the regression line.

Where appropriate the chi-square test was used to assess toxicity. Survival and remission duration were calculated using the Kaplan–Meier method. Comparison of these curves was by the log-rank test [31]. The level of statistical significance was <0.05 unless otherwise stated.

RESULTS

The study commenced in March 1984. The characteristics of the first 60 patients to complete therapy are shown in Table 1. There were no significant differences in the distribution of patients in the three treatment arms.

Toxicity

Gastrointestinal. Nausea and vomiting was more severe in the cisplatin treated patients. The overall median WHO grade was 3 for cisplatin, and 2 for the other analogues (K–W test $P = 0.0005$). The duration of vomiting (Fig. 1a) showed no change over time with iproplatin or carboplatin (LR $P > 0.2$, $P > 0.4$ respectively), however, with cisplatin there was a gradual significant increase in the duration of vomiting with successive courses of chemotherapy (LR slope +ve, $P < 0.003$). One patient discontinued cisplatin therapy after the fifth course because of intractable vomiting.

Diarrhoea was reported by 15/21 (71%) patients on iproplatin, 4/20 (20%) on carboplatin and 4/19 (21%) on cisplatin ($P < 0.0006$).

Alopecia. The number of patients with alopecia was not significantly different between the three

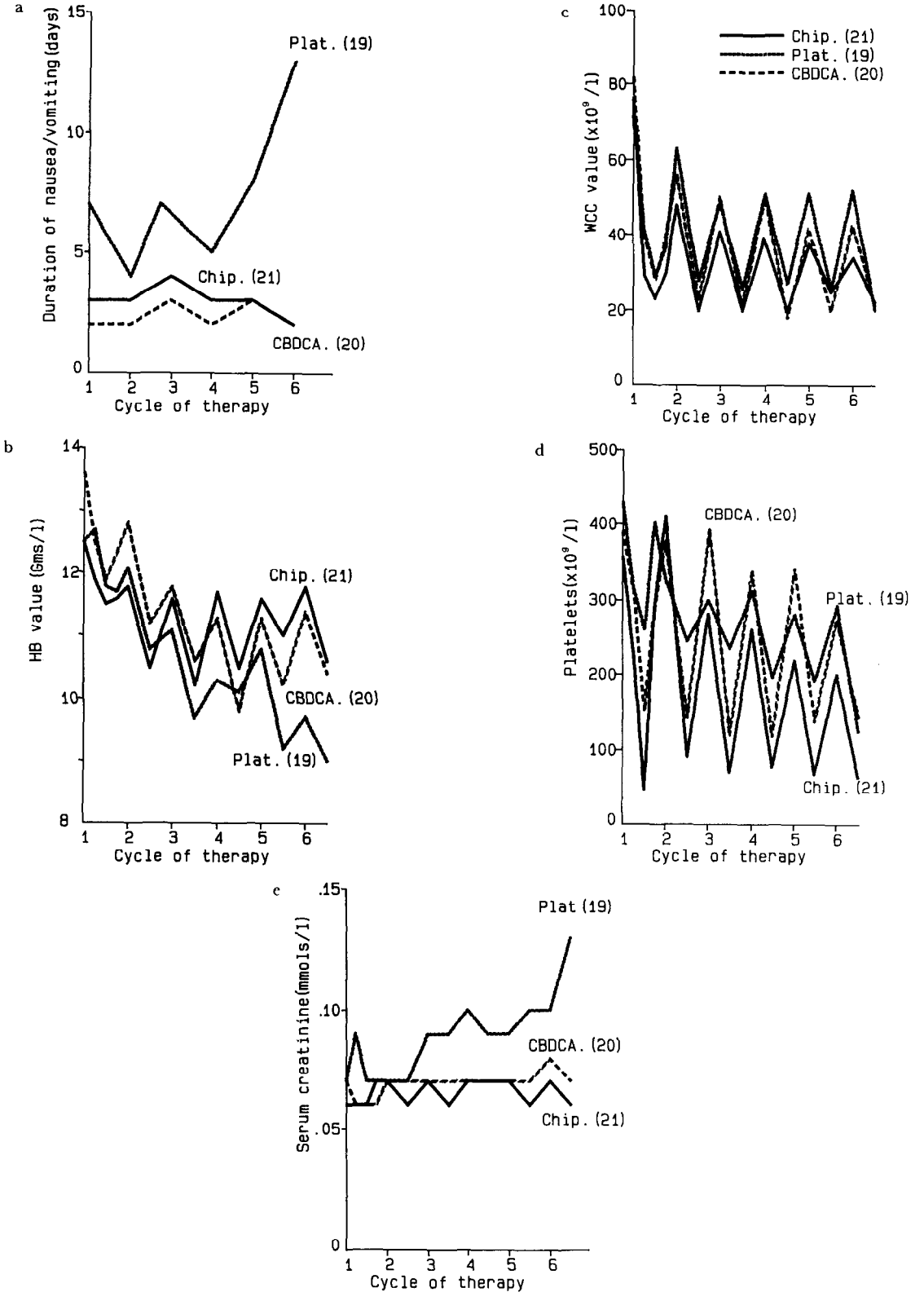

Fig. 1. Toxicity of cyclophosphamide plus platinum analogue on duration of nausea and vomiting (a), haemoglobin (b), leukocyte count (c), platelet count (d) and serum creatinine (e).

treatment arms. Alopecia occurred in 18/19 (95%) patients treated with cisplatin, 18/21 (86%) on iproplatin and 16/20 (80%) on carboplatin. The median WHO grade was 3 for cisplatin, and 2 for each of the other analogues ($P < 0.02$).

Myelotoxicity. The maximum WHO grade was recorded for each patient, and the median value taken for each treatment group. The median WHO grade for haemoglobin (Hb) was 2 for both cisplatin and iproplatin, and 1 for carboplatin. More patients

Table 1. Patient characteristics

	Cyclophosphamide therapy plus		
	Cisplatin	Iproplatin	Carboplatin
No. patients	19	21	20
Mean age (years)	52	53	55
FIGO stage			
IIb	1	1	1
IIc	3	1	3
III	9	15	9
IV	6	4	7
Histology			
well diff.	6	5	5
mod.	6	4	4
poorly	7	12	11
Bulk >2 cm			
yes	14	15	16
no	5	6	4
Ascites present	4	7	5
Karnofsky score			
60,70	4	7	3
80,90	15	14	17

on cisplatin required blood transfusions 10/19 (53%), compared with 6/21 (29%) patients treated with iproplatin and 2/20 (10%) treated with carboplatin (Table 2).

The median WHO grade for leukocyte count was 3 for all three patients. Infections were not a problem. One patient in each arm needed oral antibiotics for a mild infection. One patient was given intravenous antibiotics when she developed a faeculent peritonitis. The leukocyte count fell to 0.8×10^9/l, and she died on the 10th day after the first cycle of cisplatin.

The median WHO grade for platelet count was 4 for iproplatin, 1 for carboplatin and 0 for cisplatin treated patients. Only two patients needed platelet transfusions, both had received iproplatin therapy.

Statistical analysis was performed on WHO coded data and raw data. Similar results were obtained but the latter were more sensitive. As the raw values contain more information these data are presented.

The baseline Hb, WCC and platelet counts before therapy were not significantly different between the three treatment groups (K–W $P > 0.1$, $P > 0.3$, $P > 0.4$). Each individual and each group showed a significant pattern with time, in that the values dropped after each course of therapy and rose again by the time the next course was due (Friedman's test followed by Wilcoxon tests $P < 0.0005$ for Hb, WCC and platelets) (Figs. 1b,1c,1d). The degree of fall in Hb was significantly greater for cisplatin compared with iproplatin and carboplatin. Carboplatin was not significantly different from iproplatin (K–W followed by M–W tests $P < 0.0005$). For WCC cisplatin was significantly less toxic than iproplatin. Carboplatin fell between iproplatin and cisplatin in toxicity, but was not significantly different from either (K–W followed by M–W tests $P = 0.0005$). Iproplatin caused more thrombocytopenia than cisplatin and carboplatin, which were of equal toxicity (K–W followed by M–W tests $P < 0.0005$). All three treatments caused cumulative toxicity for Hb (LR slope −ve $P < 0.001$ for each treatment). All three treatments caused cumulative toxicity for WCC (LR slope −ve $P < 0.0005$ for each treatment), and also for platelets (LR slope −ve, $P < 0.0005$ for each treatment).

Renal toxicity. A raised serum creatinine was seen in eight patients on cisplatin (WHO grade 1 in two patients, and grade 2 in five patients; the final patient died of ovarian cancer and faeculent peritonitis). One patient on iproplatin developed WHO grade 1 renal toxicity with a raised serum urea, but a normal serum creatinine. No patients on carboplatin had renal toxicity.

Statistical analysis was performed on WHO and raw values of serum creatinine and the latter is presented. Data on creatinine clearance is not presented owing to missing data (several patients forgot to do one of their collections 2 weeks after therapy). There was no difference in the pretreatment values of serum creatinine between the three groups (K–W $P > 0.2$). The pattern of change showed a small fall after most courses of iproplatin, followed by a return to baseline at the time of the next course of therapy (Friedman's $P = 0.03$, LR slope +ve, $P > 0.7$). There was a significant gradual progressive overall rise in the serum creatinine in cisplatin treated patients (Friedman's $P < 0.002$, LR slope

+ve, $P < 0.0005$), and no change with carboplatin (Friedman's $P > 0.06$, LR slope +ve, $P > 0.09$) (Fig. 1e).

Neurological toxicity. Paraesthesiae were reported by 12 patients treated with cisplatin, three on iproplatin and three on carboplatin ($P = 0.0007$). The median WHO grade was 1 for each treatment arm. The median time of onset was course 3 for cisplatin treated patients (range 1–6). Paraesthesiae reported by patients treated with iproplatin or carboplatin were transient whereas those reported for cisplatin were initially transient and gradually lasted longer following each course of therapy until it became continuous.

Tinnitus was reported by 16 patients on cisplatin (intermittent in 12, continual in four with a median time of onset after the first course of therapy), three on iproplatin (all intermittent, one reported after first course only, the other two after the 3rd, and 4th courses) and eight on carboplatin (all intermittent, most after the 3rd and 4th courses) ($P > 0.0005$). Caloric function tests were done before and after therapy in 19 patients, and were abnormal in only one patient who complained of continual tinnitus and had received cisplatin.

Deafness was reported by nine patients on cisplatin (six had abnormal audiograms, three had no audiometry), one patient on iproplatin (no audiograms done) and two patients on carboplatin (both had normal audiograms) ($P = 0.0018$). A total of 19 pre- and post-therapy audiograms were done and six showed high tone hearing loss (all in cisplatin treated patients) (Table 4).

Dosage modification

Delays in chemotherapy were seen in three patients on cisplatin due to a low creatinine clearance (at courses 3,3,5), eight patients on iproplatin due to low leukocyte counts (median course 5, range 3–6), and five patients on carboplatin, two with leukopenia and three with a low creatinine clearance (median course 5, range 2–6).

Dose reductions in chemotherapy were required in nine patients on cisplatin (five low creatinine clearance, two leukopenia, two thromocytopenia), 19 patients on iproplatin (18 thrombocytopenia and one leukopenia), and nine patients on carboplatin (six thrombocytopenia, two leukopenia and one combined thrombocytopenia and leukopenia). The median cycle for which dose reduction occurred was five for cisplatin (range 3–6), cycle 3 for iproplatin (range 2–6), and cycle 4 for carboplatin (range 2–6). The median (mean) doses of drug received was 100% (92%) for cisplatin, 80% (79.5%) for iproplatin, and 100% (93%) for carboplatin.

Response to therapy

Tumour response is shown in Table 2. There were 10 patients who were not assessable for response (MRD—eight, early death—two). The complete plus partial remission rates were 11/14 (79%) for cisplatin, 14/19 (74%) for iproplatin, and 9/17 (53%) for carboplatin. There was no significant difference in the response rates, and although the overall response rate to cyclophosphamide and carboplatin was less than the other two trial combinations, there were more complete remissions in this group. At a median duration of follow-up of 27 months there was no significant difference in survival (Fig. 2) or freedom from progression (Fig. 3) according to therapy given.

DISCUSSION

The aim of this study was to determine the toxicity profile of two new platinum analogues and compare them with that of cisplatin when used in combination with cyclophosphamide. If the study showed roughly equal efficacy, but less toxicity, it would provide valuable information allowing the substitution of one of the new analogues for cisplatin in combination chemotherapy regimens, in an attempt to reduce chemotherapy associated toxicity.

This randomized study shows no evidence of a significant difference between the combinations in response rate, freedom from progressions or overall survival at the time of reporting when median follow up is 27 months. A randomized phase III study of cisplatin vs. carboplatin showed similar response rates [32].

Patients' subjective toxicity—intensity and duration of nausea and vomiting, alopecia and neurological toxicity—was greater for cisplatin treated patients. There was no significant difference in subjective toxicity between iproplatin and carboplatin treated patients, with one exception, iproplatin caused transient diarrhoea despite prophylaxis. Although this was of short duration (usually less than 24 h) the urgency caused some patients distress as occasionally incontinence occurred. Codeine phosphate was given prophylactically to all patients in this study before chemotherapy was given, thus the true incidence of diarrhoea may be greater than that recorded.

The paraesthesiae and tinnitus reported by patients on the new analogues were mild and transient, unlike that of cisplatin which was cumulative. Tinnitus and hearing loss have been reported with carboplatin [33], although others report that ototoxicity is not a problem [34].

The haematological toxicity was greater for iproplatin than carboplatin, indicating that equitoxic doses of these agents were not used. Dose modifications were made according to the nadir blood count. Thus cumulative toxicity data are valid and did not show that both iproplatin and carboplatin caused cumulative platelet toxicity which was greater for iproplatin. Cumulative leukocyte toxicity also occurred and was similar for carboplatin and iproplatin. Cisplatin caused more cumulative tox-

Table 2. Response to therapy

	Cyclophosphamide therapy plus		
	Cisplatin	Iproplatin	Carboplatin
Complete remission	3	4	7
Partial	8	10	2
Stable	1	0	4
Progression	2	5	4
Not assessable	4	2	2
Early death	1	0	1

Table 3. Toxicity according to median WHO grade unless stated

	Cyclophosphamide therapy plus		
	Cisplatin	Iproplatin	Carboplatin
Nausea and vomiting	3	2	2
Duration (days)	7	3	2
Alopecia	3	2	2
Number of patients	19	17	16
Hb	2	2	1
WCC	3	3	3
Platelets	0	4	1
Blood transfusions*	10	6	2
Platelet transfusions*	0	2	0

*Number of patients.

Table 4. Toxicity (continued). Number of patients with toxicity

	Cyclophosphamide therapy plus		
	Cisplatin	Iproplatin	Carboplatin
Diarrhoea	4	15	4
Neurological			
tinnitus	16	2	8
deafness	9	1	2
abnormal audiograms	6/7	0/3	0/9
abnormal calorics	1/7	0/3	0/9
paraesthesiae	12	3	2
Renal toxicity	8	1	0
Delays in therapy	3	8	5
Dose reductions	9	19	8

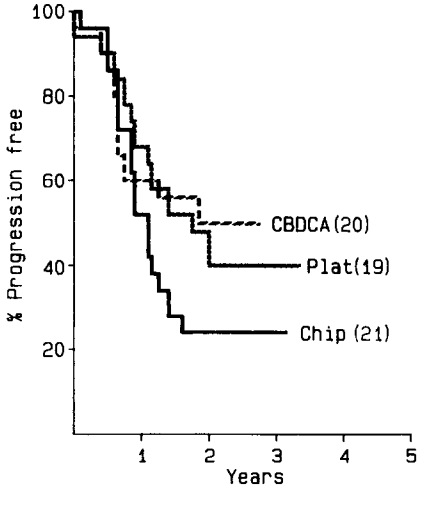

Fig. 2. Log-rank analysis of survival according to therapy given.

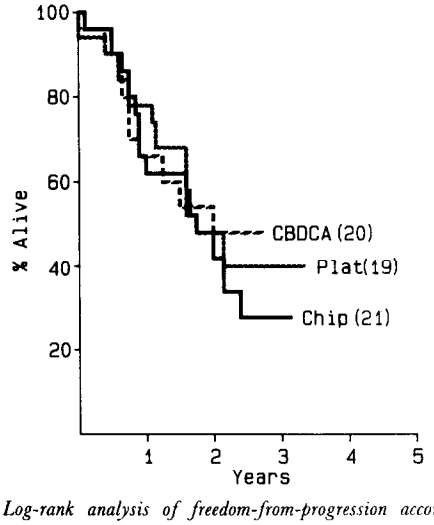

Fig. 3. Log-rank analysis of freedom-from-progression according to therapy given.

icity for erythrocytes. These results have implications in clinical management of patients on long term therapy. The median dose of analogue received was 80% for iproplatin and 100% for carboplatin and cisplatin. This leads us to recommend that in further studies using iproplatin in combination chemotherapy regimens the dose of iproplatin should be 200 mg/m^2. A phase II study of iproplatin and cyclophosphamide recommends 180 mg/m^2 [35].

Serum creatinine was used to assess renal toxicity. It is not as sensitive as other methods, e.g. creatinine clearance, and renal toxicity has probably been underestimated in this study. The reported advantage of the new analogues is lack of renal toxicity. Statistical analysis did show evidence of cumulative renal toxicity for cisplatin. The new analogues were given without post-hydration, and as emesis is mild the patients could receive this combination chemotherapy regimen as an out-patient.

In summary iproplatin and carboplatin appear to be as effective as cisplatin when given in combination with cyclophosphamide in advanced epithelial ovarian cancer. The toxicity profiles have shown that the analogues are less toxic than cisplatin. Iproplatin is more toxic than carboplatin in causing diarrhoea, and thrombocytopenia. Neither analogue caused clinical renal toxicity. Either of these two analogues could be substituted for cisplatin in combination chemotherapy regimens, with reduction in toxicity.

Acknowledgements—The authors thank Bristol Myers for supplying iproplatin and carboplatin.

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