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Original article

Weekly cisplatin and oral etoposide as treatment for relapsed epithelial ovarian cancer

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Summary

Background: Response rates to chemotherapy in relapsed, platinum resistant epithelial ovarian cancer remain poor. We have explored the effectiveness of weekly cisplatin combined with prolonged oral etoposide in this patient group.

Patients and methods: Forty-two women with relapsed, advanced ovarian cancer were treated with cisplatin 60 mg/m^2 on days 1, 8, 15, 29, 36 and 43 and oral etoposide 50 mg given from day 1–14 and day 29–43. In those who were responding and tolerating treatment (n = 13) oral etoposide 50 mg was continued for two further cycles (days 1–21 repeated every 28 days). The interval since last platinum containing chemotherapy was > 6 months in 28 patients and < 6 months in 16 patients.

Results: Thirty-six patients were evaluable for response according to CA 125 criteria giving an overall response rate of 44%. The response rate in evaluable patients declined with increasing numbers of previous treatments: 57% with one prior treatment, 42% with two, 40% with three or more. The response rate in patients who had received platinum chemotherapy within six months prior to treatment was 46%. The only significant non-haematological toxicity was nausea and vomiting in 4 patients who experienced greater than grade 2 toxicity. The number of patients experiencing haematological toxicity more than grade 2 was as follows: haemoglobin 3, white blood count 12, platelets 6. Sixteen patients had dose delays and two had dose reductions.

Conclusion We conclude that this short but intensive regimen provides worthwhile response rates, even in those patients who would ordinarily be considered refractory to platinum, and has an acceptable toxicity profile.

Key words: CA 125, cisplatin, etoposide, ovarian cancer, relapse

Introduction

Chemotherapy for relapsed ovarian cancer is palliative and the choice of drugs is determined by the previous therapy. The majority of patients will have received first line chemotherapy with a platinum compound and the probability of further response upon relapse is related to the platinum free interval [1]. Those patients with a disease free interval of more than six months are regarded as platinum sensitive and response rates of 25%–77% may be achieved using further platinum treatment [1–3]. Relapse within six months is considered to imply platinum resistance and the use of alternative agents may be justified. Many drugs including vinoralbine, altretamine, liposomal doxorubicin, oxaliplatin and gemcitabine have been assessed in phase II clinical trials in resistant disease and have not achieved response rates above 30% [4]. Taxol and topotecan have been compared in a phase III trial of second line treatment and demonstrated an overall response rates of 20.5% and 13.4% respectively [5]. With such poor results the evaluation of novel drugs and combinations is justified.

Oral etoposide used as second line chemotherapy has been shown to have an overall response rate in the region of 25% in platinum-resistant patients [6–8]. Furthermore the toxicity profile is favourable when used in selected patients. Higher response rates have been reported when oral etoposide was combined with weekly cisplatin even in 'platinum resistant' disease [9]. This led us to assess the efficacy and toxicity of this combination in women with relapsed ovarian carcinoma who have had up to four previous chemotherapy regimens and in many cases progressed during or shortly after platinum based chemotherapy.

Patients and methods

Women with relapsed epithelial ovarian cancer were treated with weekly cisplatin and oral etoposide according to the treatment schedule: cisplatin 60 mg/m^2 on days 1, 8, 15, 29, 36 and 43 and oral etoposide 50 mg given from day 1–14 and from day 29–43. Prior to the cisplatin patients received pre-hydration with at least 1 l NaCl containing 1 g $MgSO_4$ and a diuresis was induced with 500 ml mannitol 10% given over 1 h. Cisplatin was delivered in 1000 ml 2.8% NaCl over two hours. In those who were responding and tolerating treatment (n = 13) oral etoposide was continued for a further two cycles (etoposide 50 mg day for 21 days of a 28 day cycle).

All patients had received prior platinum containing chemotherapy and been treated with between one and four prior cycles of chemotherapy

Response was defined according to CA 125 criteria that have been validated by comparison with conventional response criteria [10, 11]. In brief a 50% response required four CA 125 levels, two initial

elevated samples followed by a third showing a 50% decrease and a fourth confirmatory sample. A 75% response required only three CA 125 levels with a serial decrease of at least 75%. In both 50% and 75% response definitions, the final sample had to be at least 28 days after the previous sample. A response was recorded if either a 50% or 75% response occurred

Progression was defined either by conventional objective response criteria or by CA 125. Progression according to CA 125 has been validated for defining relapse after first line chemotherapy [12, 13]. In the current study progression according to CA 125 was defined as a doubling of the CA 125 value from the nadir achieved following a response, ideally with a confirmatory sample. The date of progression was the date of the earliest event indicating progression either according to CA 125 or standard criteria. The progression free survival was the time between the start of chemotherapy and the date of progression. Toxicity was graded according to National Cancer Institute common toxicity criteria.

Results

Fourty-two women were treated between February 1996 and August 1999. All had clinical and/or radiological evidence of disease progression and none were treated solely on the basis of a rising CA 125. Two patients were treated with the regimen on two separate occasions and the denominator for response is therefore 44. The patient characteristics are shown in Table 1. Thirty-five (83%) women had received two or more chemotherapy regimens and 16 (38%) had received platinum based chemotherapy within the previous six months. This population was therefore a relatively heavily pre-treated group many of whom would be considered platinum resistant.

Table 1 Patient characteristics ($n = 42$)

Age (years)	
Median	58
Range	34–81
Histology	
Serous	26
Mucinous	2
Endometroid	2
Clear cell/mesonephroid	1
Mixed	2
Unclassified	9
Number of prior chemotherapy regimens	
1	9
2	21
$\geqslant 3$	14
Interval since previous chemotherapy	
Median (days)	114.5
Range	7–494
Interval since last platinum containing chemotherapy	
Median (days)	231
Range	26–794
< 6 months (no. patients)	16 (median = 120 days, range 26–179)
> 6 months	28 (median = 312 days, range 181–794)

Response

A median of five doses of cisplatin was given to each patient (range 1–6) with 17 receiving the full six doses. A median of 28 doses of etoposide was given (range 4–91). Thirty-six patients were evaluable for response according to CA 125 criteria and 16 of these achieved a response, giving an overall response rate of 44%. Eight patients were non-evaluable for response according to CA 125 criteria, seven because less than three samples were available for analysis and one in whom all CA 125 values were < 40 U/ml. If all non-evaluable patients were included in the analysis according to intention to treat (ITT), and classified as non-responders, the response rate was 36%. The median overall survival of the whole group was 6.6 months (Figure 1). Median progression free survival according to standard or CA 125 criteria was 3.68 months (Figure 2).

In those 16 patients who responded to treatment the median survival was 11.1 months while the survival in those who did not respond or were non-evaluable was 5.5 months and 3.1 months respectively (Figure 3). The difference in survival between the responders and

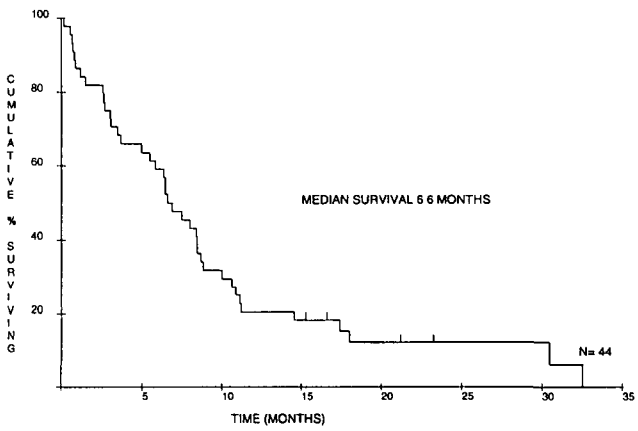

Figure 1. Kaplan–Meier curve to show survival from date of start weekly cisplatin regimen

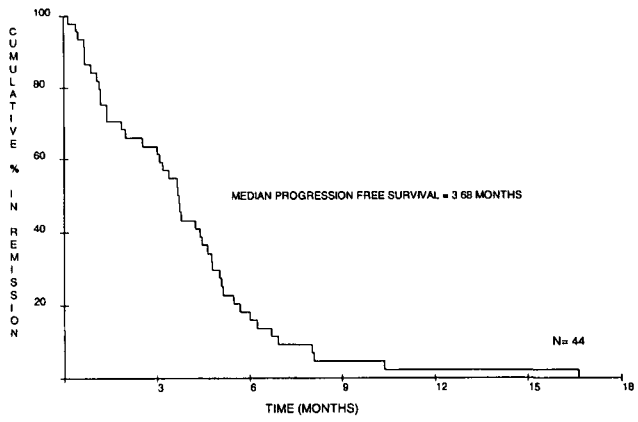

Figure 2. Kaplan–Meier curve to show progression free survival from date of start weekly cisplatin regimen. The date of progression was the date of the earliest event indicating progression according to either CA 125 or standard criteria.

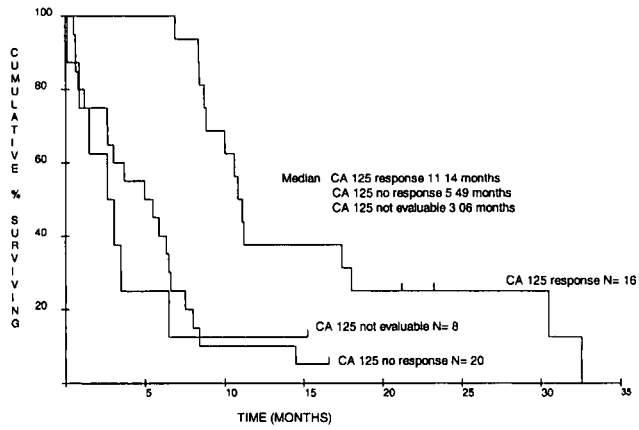

Figure 3 Kaplan–Meier curves showing survival by CA 125 response from date of start weekly cisplatin regimen.

Table 2 Response rates according to CA125 response criteria.

Overall response rate (n = 36)	44%
Response rates according to number of prior chemotherapy regimens	
1 (n = 7)	57%
2 (n = 19)	42%
$\geqslant$3 (n = 10)	40%
Response rates according to platinum free interval	
<6 months (n = 13)	46%
>6 months (n = 23)	43%

non-responders was highly significant ($P < 0.001$). This suggests that objective response translated into improved survival and that those who were non-evaluable were non-evaluable because poor response precluded the collection of sufficient samples to assess response.

As might be anticipated the response rate tended to decrease with increasing numbers of prior chemotherapy regimens from 57% (44% ITT) for first relapse treatment to 40% (29% ITT) in patients who had received three or more prior regimens (Table 2). The response rate and median survival in those who had previously received platinum within the previous six months (RR 46%, median survival 6.34 months) was equivalent to that in those who had been treated after an interval of greater than six months (RR 43%, median survival 6.9 months).

Toxicity

The worst grade of toxicity that was experienced by each patient throughout the course of chemotherapy was recorded (Table 3). Blood counts were taken before each dose of cisplatin. As shown in Table 3, 14 patients (32%) developed more than grade 2 leucopenia while six (14%) developed more than grade 2 thrombocytopenia. Only six (14%) patients developed more than grade 2 non-haematological toxicity with five (11%) patients developing grade 3 or 4 vomiting and one (2%) developing grade 3 ototoxicity. Sixteen (37%) patients had a dose delay and two (5%) had dose reductions.

Discussion

This was not a prospective phase II study but a retrospective analysis of a single chemotherapy regimen used to treat a heterogeneous group of relapsed ovarian cancer patients. Both the response data and the toxicity were recorded prospectively and any bias inherent in the retrospective design was therefore minimised. The spectrum of patients treated was therefore more diverse and representative of a patient population typically seen in the practice of gynaecological oncology. As such it included those with relative platinum resistance and those who had progressed after multiple lines of chemotherapy, both characteristics which would tend to militate against a response to further platinum based chemotherapy. In spite of this, response rates were as good if not better than those obtained using second line drugs such as taxol and topotecan in so-called platinum refractory patients [5]. The progression free survival was relatively short (3.68 months) but the use of CA 125 as an indicator of progression is reported to have a lead time bias of 63 days [12] and therefore this figure cannot be compared with those obtained using conventional clinical criteria.

We have previously shown that a 50% or 75% decrease in CA 125 levels accurately predicted drug activity in

Table 3. Toxicity. Table shows number of patients experiencing grade of toxicity.

Toxicity	Grade 1 no. (%)	Grade 2 no. (%)	Grade 3 no. (%)	Grade 4 no (%)
Haematological				
Haemoglobin	12 (29)	16 (39)	3 (7)	0
White blood count	8 (20)	8 (20)	9 (22)	5 (13)
Platelets	16 (40)	5 (13)	4 (10)	2 (5)
Non-haematological toxicity				
Renal	2 (5)	1 (3)	–	–
Nausea and vomiting	15 (34)	11 (25)	2 (7)	3 (10)
Lethargy	19 (44)	7 (16)	–	–
Neurotoxicity	8 (18)	–	–	–
Ototoxicity	10 (23)	1 (2)	1 (2)	–

phase II trials [10, 11]. In that study the response rate according to CA 125 was slightly, but not significantly, higher than the standard response rate and no correction factor was recommended. If patients who were non-evaluable for response according to CA125 progressed within six weeks of starting treatment they could be classified as non-responders. This modification would reduce the CA 125 response rate. In our study there were eight patients who were classified as non-evaluable for response and of these four progressed within six weeks of treatment. Applying the modification described above would reduce the response rate from 44% to 40%. The remaining four were non-evaluable because they did not progress within six weeks and had less than three CA 125 values or had values that were less than 40 u/ml.

The effectiveness of the regimen could be related to the increased dose intensity of the cisplatin or the combination of cisplatin and etoposide. Early reports of dose intensification of cisplatin in ovarian cancer suggested that this strategy may be effective. Piver reported a 70% objective response rate in a small series of patients using cisplatin 1 mg/kg given weekly for six weeks followed by cisplatin 60 mg/m^2 given as third line treatment [14]. This contrasted with a 5% response rate using 100 mg/m^2 three-weekly reported in a previous series of similar patients by the same authors [15]. Subsequently the role of dose intensity has been examined in a meta-analysis and, in contrast to other agents, there was a statistically significant association between complete and partial response and the dose intensity of cisplatin used as first line treatment [16, 17]. This only applied to a dose of up to 25 mg/m^2/wk and above this level the dose response curve appeared to flatten. Several individual trials have also examined the question of dose intensity using the same total dose or an increased total dose. The Gruppo Interegionale Cooperativo Oncologcio Ginecolgia (GICOG) randomised patients with advanced ovarian cancer to either six cycles of cisplatin 75 mg/m^2 every three weeks or nine cycles of cisplatin 50 mg/m^2 every week and found no significant difference in response rates or progression free and overall survival [18]. Several trials in which the total dose of platinum was increased in addition to dose intensity have also failed to yield improved response rates or survival [19, 20]. In contrast the study by Kaye et al. demonstrated improved response rates and a small overall survival advantage for the combination of cisplatin 100 mg/m^2 with cyclophosphamide three weekly for six cycles over the same combination with cisplatin 50 mg/m^2 [21]. This may be explained by the fact that the doses used in this study spanned the dose range over which a dose-response relationship holds. Indeed the low dose arm yielded inferior results by comparison with other trials.

The use of stem cell support has enabled the safe delivery of even higher doses of platinum but as yet there are no reported randomised trials. Stiff reported a progression free survival of seven months and overall survival of 13 months for 100 patients treated with a high dose chemotherapy regimen containing carboplatin up to a dose of AUC of 28 [22]. However, among those with platinum resistance and a tumour bulk of more than 1 cm, the median overall survival was only 8.6 months. The question of dose intensity has not been systematically addressed in platinum refractory disease and it may be that a dose response relationship exists for doses above 25 mg/m^2/wk in this sub-group. In summary it seems unlikely that the dose intensity of cisplatin alone accounts for the high response rates seen in our study but the intense scheduling does allow effective treatment to be delivered over a shorter period.

Prolonged oral etoposide has yielded response rates of about 25% in platinum refractory patients [6–8]. In one trial, for which CA 125 data was available, the response to oral etoposide was 29% by standard criteria and 21% by CA 125 criteria [11]. The prolonged oral dose schedule is rational based on the phase specificity of the drug and gives results superior to those obtained using three weekly regimens even when combined with carboplatin [23].

In her initial report, using a combination of weekly cisplatin and oral etoposide, van der Burg presented response rates of 38%, 78% and 93% for those who had progressed within 0–3, 3–6 and 6–12 months respectively [9]. In contrast we found response rates for those treated with a platinum free interval of more or less than six months to be equivalent although there was a trend toward reduced efficacy with increasing number of previous chemotherapy regimens. Those treated with <6 month platinum free interval had received slightly less chemotherapy previously (mean 2.12 regimens per patient) compared to those with a >6 month platinum free interval (2.63 regimens per patient). The median interval since previous platinum containing chemotherapy was 231 days yet it was only 115 days since any previous chemotherapy. If there was more use of regimens without platinum in our patients than in those reported by van der Burg this might explain the differences in response rates between the two studies but equivalence in response rates between the two groups in our study. Nevertheless, in this study, we have confirmed a high response rate both in platinum resistant disease and in those who have received multiple lines of treatment. Furthermore the regimen has the advantage of being short and well tolerated in the majority of patients.

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