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Original Paper

A Phase II Study of Carboplatin and Hexamethylmelamine as Induction Chemotherapy in Advanced Epithelial Ovarian Carcinoma

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27 patients with ovarian cancer FIGO stages IIc–IV were treated with carboplatin 7 × (glomerular filtration rate + 25) mg given intravenously on day 1 and hexamethylmelamine (HMM) 150 mg/m² orally on days 2–15, every 28 days. 3 patients were not evaluable for response. Clinical response was seen in 17 patients (71%), with six (25%) complete and 11 (46%) partial responses. The median progression-free survival was 15.6 months and the median cancer-related survival was 21.3 months. 4 patients (15%) experienced grade 3 mental depression; none had peripheral neuropathy above grade 1. The haematological toxicity was moderate, none had grade 4 leucopenia, but 4 (15%) had grade 4 thrombocytopenia. Carboplatin plus HMM had few side-effects and a high response rate with a survival comparable to other platinum-based combinations.

Key words: ovarian cancer, combination chemotherapy, carboplatin, hexamethylmelamine
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INTRODUCTION

CISPLATIN IS the most active single agent in advanced ovarian cancer, and has become part of the standard treatment of this disease, however, several reports suggest carboplatin to be as effective but less ototoxic, neurotoxic, nephrotoxic and emetogenic [1]. Hexamethylmelamine (HMM) has considerable activity in tumours that are resistant to platinum [2]. Used as single agent in first-line chemotherapy, response rates of 31–42% have been reported [3], and when incorporated in multiple drug regimens superior long-term survival has been observed [4], especially in the subgroups of patients with smaller tumour burdens.

PATIENTS AND METHODS

Patient eligibility was defined by age between 18 and 80 years, and ECOG performance status of at least 2, a glomerular filtration rate (GFR) above 50 ml/min, a normal white blood cell (WBC) and platelet count (PLC) and normal liver functions. No previous chemotherapy was allowed and treatment had to start within 6 weeks after primary surgery.

Treatment and dose modification

Carboplatin was given as 7×(GFR + 25) mg on day 1 and Hexalen (HMM) 150 mg/m² days 2–15 divided into four oral doses, every 4 weeks for six courses, with additional three courses as an option. The dose of carboplatin was reduced by 25% in the case of WHO grade III and by 50% in the case of WHO grade IV leuco- or thrombocytopenia at nadir. Haemoglobin level, WBC and PLC were determined weekly, liver and kidney function before every course. If treatment had to be delayed for more than 2 weeks, the patient was taken out of the study.

Response evaluation

Response and toxicity were evaluated according to the WHO criteria [5]. Response rates are calculated on the basis of all patients with measurable tumour before chemotherapy according to the principle of intention to treat.

Survival statistics

Survival and progression-free interval were calculated from the date of the first course of chemotherapy using the method of Kaplan and Meier [6]. In the calculation of progression-free survival, a change to another treatment was considered as a censoring event.

RESULTS

Patients' characteristics are presented in Table 1. The number of courses given and dose reductions for carboplatin are shown in Table 2. 3 patients received only one course, 2 because of grade 3 mental depression and 1 because of early progression of disease. In cycles four to six, the dose had to be reduced in most of the cycles, but most often to 75–90% of the projected dose and only in 5–10% of cases to 50%. The reason for dose reduction was low nadir values for both PLC and WBC in 4 patients, low

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Table 1. Characteristics of 27 patients

	No. of patients	%
FIGO stage		
IIc	2	7
IIIb	1	4
IIIc	8	30
IV	16	59
Histological type		
Serous	23	85
Mixed serous/mucinous	1	4
Clear cell	1	4
Undifferentiated	2	7
Degree of differentiation		
High	3	11
Moderate	6	22
Poor	18	67
Residual tumour after surgery		
None	2	7
Diffuse carcinomatosis	3	11
≤2 cm	3	11
>2 – <5 cm	4	15
≥5 cm	15	56
Age (years)		
40–50	3	11
51–60	5	18.5
61–70	14	52
71–80	5	18.5

Table 2. Dose of carboplatin delivered

Cycle no.	No. of patients	Per cent of projected dose 110	100	75–90	50
1	27	0	27	0	0
2	24	3	17	4	0
3	23	2	15	5	1
4	21	2	5	13	1
5	20	0	2	17	1
6	17	0	1	14	2
7	11	0	1	8	2
8	8	0	1	5	2

PLC nadir in 16 patients and low WBC nadir in 3 patients. 2 patients went off study because of cycle prolongation of more than 2 weeks. The mean cycle duration was 31.8 days. There were no cases of WHO grade 4 leucopenia, but 4 cases of WHO grade 4 platelet toxicity.

4 patients (15%) experienced mental depression WHO grade 3, 2 of them in the first treatment cycle and 2 in the second. All diagnoses were confirmed by a psychiatrist. Cessation of HMM treatment resulted in complete resolution of the symptoms. Only 1 of the 5 patients had a history of depression. There was 1 case of severe emesis during HMM intake, responding partially to treatment with ondansetron; the patient completed six courses. There was 1 case of peripheral neuropathy of low grade that disappeared after treatment was stopped. Ototoxicity or nephrotoxicity was not observed.

Only 24 patients were evaluable for response, as 3 patients had no measurable disease before the start of chemotherapy. The overall response rate was 71% (6 patients (25%) complete response and 11 patients (46%) partial response). Stable disease occurred in 1 patient (4%) and progressive disease in 4 (17%), while 2 (8%) were non-evaluable. The median progression-free survival was 15.6 months and the median corrected survival was 21.3 months. The median follow-up for patients still alive was 22.3 months.

DISCUSSION

The study group contains patients with an over-representation of poor prognostic factors such as FIGO stage IV, large residual tumours after primary surgery and poorly differentiated tumours. Nevertheless, the overall clinical response rate of 71% and corrected median survival of 21.3 months compare favourably with those found in other studies with HMM-containing regimens [4, 7, 8] and carboplatin combinations [9, 10].

The frequency of non-haematological toxicity was low, but noteworthy is the occurrence of 4 cases of grade 3 mental depression. The symptoms resolved after treatment was discontinued. One of these patients had a history of depression. The frequency of mental depression was higher in this study than in our study on HMM as second-line therapy [2], using a higher dose of HMM. In previous reports on HMM in combination chemotherapy [4, 7], mental depression was not reported. This discrepancy may be explained by the small number of patients in our study. As could be expected with a combination chemotherapy containing carboplatin, bone marrow depression was common, but in most cases only of grade 1 or 2.

Thrombocytopenia grade 4 occurred in 4 patients (14%), while no cases of grade 4 neutropenia occurred. In most cases, bone marrow toxicity led to dose reduction but not before the fifth course and a dose reduction to 75–90% of projected carboplatin dose was sufficient. The mean cycle duration was only slightly prolonged due to bone marrow toxicity; 31.8 days instead of the planned 28 days. It should be taken into account that 70% of the treated patients were more than 60 years old and such patients required dose reductions for continuation of treatment more often than younger patients [11].

The bone marrow toxicity in our study corresponds quite well with the reported figures from the carboplatin (300 mg/m^2) plus cyclophosphamide (600 mg/m^2) arm in two larger randomised studies comparing cisplatin plus cyclophosphamide to carboplatin plus cyclophosphamide in advanced ovarian cancer [9, 10]. Although the delivered carboplatin dosages are not directly comparable, we have probably delivered a higher carboplatin dose.

In conclusion, this study shows that the combination of carboplatin and HMM in first-line treatment of ovarian cancer was feasible and resulted in high response and survival rates comparable to other first-line platinum-based combination chemotherapies.

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