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cis-Dichlorodiammineplatinum (II) and Hexamethylmelamine in Advanced Ovarian Carcinoma: A Phase II Study

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Abstract—*Thirty-eight previously treated patients with ovarian carcinoma received a combination of* cis-*dichlorodiammineplatinum (II) (CDDP) and hexamethylmelamine (HMM). The schedule was CDDP* 75 mg/m² *i.v. with forced diuresis on day 1, followed by HMM* 200 mg/m² *p.o. on days 8–21, repeated every* 4 weeks. *In 29 evaluable patients an overall response rate (CR + PR) of* 35% *with a median response duration of* 4.5 months *was observed. The performance status seemed to be an important prognostic factor. The gastrointestinal- and neurotoxicities were severe and resulted in dose modification and/or drug discontinuation in half of the patients. In conclusion, CDDP and HMM is an active drug combination in advanced ovarian carcinoma resistant to conventional chemotherapy. A possible superiority of this combination compared with CDDP or HMM alone has to await randomized trials.*

INTRODUCTION

IN OVARIAN carcinoma the alkylating agents have been used extensively, resulting in objective response rates of about 50%, but also other agents, including adriamycin, 5-fluorouracil and methotrexate, have shown activity [1, 2]. The response rates of the different agents when used as second- and third-line therapy are, however, disappointingly low [3, 4].

In recent years drugs such as *cis*-dichlorodiammineplatinum (II) (CDDP) and hexamethylmelamine (HMM) have also shown promising activity in patients previously treated with chemotherapy [1]. Davis *et al.* reported an objective response rate of 57% with 20% complete remissions using a combination of CDDP and HMM in 22 previously treated patients [5].

The purpose of this study was to explore further the activity of a combination of CDDP and HMM in previously treated patients with ovarian carcinoma.

MATERIAL AND METHODS

Patients included in the study had histologically proven cystadenocarcinoma or undifferentiated ovarian carcinoma FIGO stages III and IV, clinically resistant to conventional therapy. In order for patients to enter the trial their disease had to be progressive within the last two months and with at least one measurable lesion. Pleural effusions, ascites and osseous and CNS metastases were not accepted as measurable disease. Lesions visualized by ultrasound or computerized axial tomography were only considered evaluable provided that their malignant nature was verified histologically or cytologically.

The performance status was graded from 0 to 4 according to the WHO scale [6]. A patient was regarded eligible if the expected survival was at least 2 months. Prior chemotherapy should be terminated at least 3 weeks before entry in the study. No patients had received radiotherapy for at least 6 months before entering the study. B leukocytes $\geqslant 3.0 \times 10^9$/l, B thombocytes $\geqslant 100 \times 10^9$/l, creatinine < 100 μmol/l and a normal [^{51}Cr]-EDTA clearance were mandatory. Initial work-up included physical and pelvic examinations, abdominal and pelvic ultrasound, intravenous pyelograms, [^{51}CR]-EDTA clearance, audiogram and chest X-ray. Serum bilirubin, serum alkaline phosphatase, serum glutamic oxaloacetic-transaminase, [^{51}Cr]-EDTA clearance, serum creatinine and pelvic examination were

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repeated monthly and blood counts prior to every treatment. Abdominal ultrasound and chest X-ray were repeated every second month and audiograms every third month. Response to therapy was assessed after every course.

The dose of CDDP was 75 mg/m^2 on day 1, followed by HMM 200 mg/m^2 from day 8 to day 21. This schedule was repeated every four weeks. Chemotherapy was modified at scheduled retreatment as follows: 100% dose: WBC $>3.0\times10^9$/l and platelets $>75\times10^9$/l; 75% dose: WBC ≥2–2.999×10^9/l and/or platelets $\geq74.999\times10^9$/l; 0% dose: WBC $<1.999\times10^9$/l and/or platelets $<74.999\times10^9$/l. Furthermore, doses were modified by 25–50% according to the severity of toxic side effects such as nausea, vomiting and paresthesias.

CDDP* was supplied as powder in 10-mg or 50-mg vials. It was dissolved in sterile water at a concentration of 1 mg/ml immediately prior to administration. Pretreatment hydration, consisting of 1500 ml isotonic saline/dextrose, was infused over a 90-min period. The drug solution was then diluted with 1000–1500 ml isotonic saline with 3.6% mannitol and infused over a period of 30–60 min. Finally, another 2000 ml saline/dextrose was infused over another period of 2 hr. Adequate hydration and urinary output was maintained during the following 24 hr. HMM† was supplied in 100-mg capsules and administered in divided daily doses one hour after mealtimes to lessen the gastrointestinal side effects.

Pyridoxin was not used as prophylactic treatment in this study. Definitions of response were identical to the WHO criteria [6], with the exception that response duration was calculated from the time of registration of response.

Patients with an objective response or stable disease were treated until progression.

All evaluable patients received at least 2 courses of therapy. Informed consent from the patient was obtained before starting the treatment with CDDP and HMM.

RESULTS

From November 1980 to June 1981 38 patients entered the study. Three patients receiving less than 2 courses of chemotherapy were excluded from the analysis because of disease progression (2 patients) and treatment refusal (1 patient). Another 6 patients were only included in the evaluation of toxicity as they had no measurable disease. Two of these altered their performance status from 3 to 0 during the treatment and are still alive at 17+ and 15+ months after start of treatment.

Among the fully evaluable 29 patients the median age was 55 yr (range 33–68) and the median performance status 2 (range 0–4) (Table 1). The median time from histologic diagnosis to start on protocol treatment was 13 months (range 4–52). Prior treatment included chemotherapy alone in 23 patients, and chemotherapy and radiotherapy in 6 patients. All patients had received alkylating agents and 27 had received adriamycin. Among the 29 patients evaluable for response the median number of courses of CDDP + HMM was 4 (range 2–11). Within a median treatment time of 2½ months (range 1–7), 8 out of 29 patients (28%) achieved a partial response with a median duration of 4 months (range 1–6). Their median performance status was 1 (range 0–3). Two patients (7%) with performance status 0 achieved a complete response of 5 and 6 months duration respectively. CR was achieved 1 and 4 months respectively after initiation of treatment (Table 2). Thus the overall response rate was 35% (95% confidence limits 18–54%). Three patients (10%) had stable disease of a median duration of 6 months (range 4–9+). These three patients received a median of 6 courses of CDDP + HMM (range 4–9+).

Table 1. Patient characteristics

No. of patients evaluable for response	29
Median age in years (range)	55 (33–68)
Median performance status (range)	2 (0–4)
Histologic subclassification:	
cystadenocarcinoma	97%
undifferentiated carcinoma	3%
Site of indicator lesions (1 or more):	
pelvis + abdomen	90%
skin	7%
lungs	10%
peripheral lymphnodes	17%
Prior chemotherapy:	
alkylating agents	100%
adriamycin	93%
others (5-fluorouracil, *m*-AMSA)	93%
Response to previous chemotherapy (CR + PR)	73%
Prior radiotherapy	21%

Table 2. Performance status compared to response rate (PR + CR) in 29 evaluable patients

Performance status	Response rate	
	No.	%
0–1	7	24
2–3	3	11
3–4	0	0

*Supplied by Bristol-Myers.

†Supplied by Laboratoire Roger Bellon S.A., Neuilly sur Seine, France.

Toxicity

The major type of toxic side effects of CDDP and HMM were gastrointestinal, hematological, neurological, otological and renal.

Twenty-eight (80%) of the 35 patients required between 25 and 50% dose modification and/or drug discontinuation because of toxicity. Neurological toxicity was the sole reason for discontinuation of the treatment in 5 patients (14%).

Hematologic toxicity

Thirteen (37%) out of 35 patients evaluable for toxicity developed both leukopenia and thrombocytopenia, with B leukocytes less than $3.0 \times 10^9/l$ and B thrombocytes below $75 \times 10^9/l$ at time of retreatment in at least one course. Three patients (9%) demonstrated only leukopenia and 8 patients (23%) only thrombocytopenia during the treatment. One patient developed prolonged thrombocytopenia of 2 months duration and another patient died due to severe thrombocytopenia and clinical bleeding with widespread metastatic ovarian carcinoma. One patient experienced recurrent septicemia. Nineteen patients (54%) required blood transfusions 1–5 times during the treatment (Table 3).

Table 3. Hematologic toxicity of CDDP + HMM in 35 previously treated patients

Lowest value	Percentage of patients
B thrombocyte counts	
$< 75 \times 10^9/l$	55
$< 50 \times 10^9/l$	28
$< 20 \times 10^9/l$	3
B leukocyte counts	
$< 3.0 \times 10^9/l$	42
$< 2.0 \times 10^9/l$	18
$< 1.0 \times 10^9/l$	0

Gastrointestinal toxicity

Six patients (17%) suffered mild nausea and vomiting, 27 patients (77%) moderate and 5 patients (14%) severe gastrointestinal toxicity. The latter was defined as almost constant nausea and vomiting for a 24-hr period after CDDP infusion. During treatment with HMM, 7 patients (20%) experienced no gastrointestinal side effects, and 16 patients mild (46%), 4 patients (11%) moderate and 11 patients (31%) severe gastrointestinal side effects. Of the latter 11 patients, 6 had from 33 to 50% reduction of the dose of HMM and in 3 patients HMM was discontinued for one course due to a combination of side effects. The median time to development of gastrointestinal side effects due to HMM was 60 days (range 7–150 days) (½–5 courses of treatment).

Neurotoxicity

Ten (29%) patients experienced peripheral neuropathy primarily as paresthesias in fingers and toes. Five of these patients developed disabling gait disturbances which made discontinuation of treatment necessary in four patients and caused the fifth patient to refuse further treatment. The symptoms were irreversible during the observation time. The median time to develop neurological side effects was 180 days (range 60–240 days) (3–8 courses of treatment).

Nephrotoxicity

Four out of 35 patients (11%) experienced a moderate decrease in [^{51}Cr]-EDTA clearance after 2 courses of CDDP. The decrease was irreversible during the observation time.

Ototoxicity

Five out of 35 patients (14%) experienced mild irreversible hearing loss, 2 unilaterally and 3 bilaterally, essentially limited to a frequency range above the speech tone (4000–8000 Hz). The median time to development of ototoxicity due to CDDP treatment was 135 days (range 90–240 days) (3–8 courses of treatment).

DISCUSSION

In this study we observed an overall response rate of 35% with a median response duration of 4.5 months with the combination of CDDP and HMM. These results are encouraging considering that they were obtained in a group of patients with a relative poor performance status, pretreated with alkylating agents, adriamycin, 5-fluorouracil and radiotherapy. The study also indicates that performance status might be an important prognostic factor, an observation also made by others [7, 8].

The dose-limiting toxicity in this study was severe gastrointestinal toxicity and neurotoxicity which seemed to be cumulative, while the hematologic toxicity was modest.

Our response results and toxicity are in the same range as found by other authors with a combination of CDDP and HMM using nearly identical doses and schedules [5, 7, 9, 10]. In these studies including 68 patients with a pretreatment and performance status comparable to ours the median response rate was 34% (range 14–80%) and the median response duration 6.5 months. Using high-dose CDDP alone, the response rate from the literature in 169 previously treated patients with ovarian carcinoma reaches a median of 32% (range 5–70%) with a median response duration of 5–6 months [8, 11–16]. In comparison, the median response rate of HMM used as single

agent in 71 previously treated patients is 17% (range 15–28%), with a median response duration of 6 months [4, 17, 18].

It is concluded from this and the above-mentioned studies that CDDP + HMM is not necessarily clinically cross-resistant to the classical drugs used in ovarian carcinoma. The great variation in response rates may be explained in patient selection and evaluation, drug schedules and definition of response criteria. Therefore the advantage of using a combination of CDDP + HMM compared with CDDP alone has to await randomized trials in patients resistant to conventional chemotherapy in advanced ovarian carcinoma.

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