Eur J Cancer Clin Oncol. Vol. 21, No. 6, pp. 665–669, 1985.
Printed in Great Britain.

0277-5379/85$3.00+0.00
© 1985 Pergamon Press Ltd.

# Adriamycin and *cis*-Platinum in Advanced Ovarian Cancer

AIMERY DE GRAMONT,* YVAN DROLET, ANDRE LAVOIE, MARC PAINCHAUD, RENE BLOUIN, CLAUDE TESSIER and PIERRE OUELLET

*Department of Hemato-Oncology, Hôtel-Dieu de Québec, Quebec City, Canada*

**Abstract**—*Forty-eight patients with stage III and IV ovarian epithelial carcinoma were treated with single doses of adriamycin (ADM)* 50 mg/m² *and* cis*-platinum (DDP)* 50 mg/m² *every month for nine courses. The pathologically proven response rate was* 52.2%, *with* 22.7% *complete response and* 29.5% *partial response. Median survival was* 22 months *for all patients,* 25 months *in stage III and* 15 months *in stage IV. This study confirms that ADM-DDP is a valuable drug regimen in advanced ovarian carcinoma but further progress is needed to improve the cure rate, which remains low.*

## INTRODUCTION

IN STAGE III and IV ovarian cancer, the major challenge remains that of improving survival duration.

The first step towards meeting this challenge was the use of alkylating agents, mainly melphalan, after surgery; this increased median survival to about 12 months with 20% of the responding patients alive after five years [1]. The second step was the introduction of polychemotherapy regimens. The most successful regimens were those using adriamycin (ADM) and the combination of hexamethylmelamine, cyclophosphamide, methotrexate and 5-fluorouracil (Hexa-CAF) [2, 3]. Median survival was between 10 and 29 months, a mean improvement of 6 months over melphalan alone, and an improvement of 1 yr in the randomized study of Young *et al.* comparing melphalan and Hexa-CAF [3]. The third step was the use of *cis*-platinum (DDP), alone or in combination, which appeared to be more effective than alkylating agents, the thiotepa and methotrexate combination and even Hexa-CAF [4–6]. Median survival observed was between 15 and 30 months [5, 7, 8]. However, it is not certain that adding other cytotoxic drugs to DDP improves the results achieved with this single agent.

Accepted 12 December 1984.

*Present address and to whom requests for reprints should be addressed: Service du Professeur J. Debray, Pavillon Moïana, Hôpital Saint-Antoine, 184, rue du Faubourg Saint-Antoine, 75571 Paris Cedex 12, France.

We report our experience with the ADM-DDP combination in previously untreated stage III and IV ovarian carcinoma following the successful results obtained with this combination by Bruckner *et al.* [9].

## MATERIALS AND METHODS

Adriamycin and *cis*-platinum (ADM-DDP) were used as the primary chemotherapy regimen in patients with advanced ovarian adenocarcinoma. Forty-eight patients with histologically proven stage III-IV (FIGO) epithelial cancer were treated with this regimen from May 1979 to January 1983.

Patients were staged according to FIGO criteria after initial surgery with an added distinction between stage IIIA: minimal residual tumors of less than 2 cm diameter; and stage IIIB: residual tumors of more than 2 cm diameter. All stage IIIA patients had the optimal surgery: total hysterectomy and bilateral salpingo-oophorectomy and omentectomy with a maximal reduction of the primary tumor. The ADM-DDP regimen consisted of adriamycin 50 mg/m² and DDP 50 mg/m² administered every month for 9 months. Adriamycin was given by slow i.v. push for a total theoretical dose of 450 mg/m² or less if toxicity occurred. DDP was administrated by a half-hour intravenous infusion after 40 mg i.v. furosemide, in 500 ml dextrose 5% with 12.5 g mannitol. Hydration was started 3 hr prior to the administration of DDP and continued for 24 hr. Adriamycin doses were reduced if leukocytes were

less than 3000/mm³ and platelets less than 100,000/mm³ before the course. DDP was not administered if serum creatinine level was over 1.5 mg/100 ml.

After nine courses, all living patients were scheduled for second-look laparotomy with removal of residual tumor or multiple biopsies if no residual macroscopic disease was present. One patient underwent surgery at 6 months for intestinal occlusion.

Treatment was stopped whenever biopsies came back negative. Patients with residual disease received either melphalan 8 mg/m² p.o. 4 days every month or melphalan 6 mg/m² p.o. 4 days and hexamethylmelamine 120 mg/m² p.o. 14 days every month.

Parameters considered were: age and performance status according to ECOG; histological type and cellular differentiation, (cellular differentiation was noted as: grade 1, well differentiated; grade 2, moderately differentiated; grade 3, poorly differentiated); initial total tumor volume of all masses and of the largest tumor; volumes were determined by the product of the largest diameter and the diameter perpendicular to it; and residual disease after surgery.

Tumor volume could not be evaluated in all patients, either because complete abdominal exploration was impossible or because the tumors were not measurable, as in the case of diffuse carcinomatosis. Most histological material was retrospectively reviewed for cytological grading when available.

Tumor responses were evaluated on pathological criteria. Clinical responses were not retained because they had shown poor accuracy in previous studies. Complete response was a total disappearance of residual macroscopic and microscopic disease. Partial response was more than 50% decrease, stable disease was less than 25% increase and progressive disease was either more than 25% increase in tumor size or appearance of new lesions. Patients who died of their disease before second look were also retained as having progressive disease. Two patients who remained disease-free at second-look laparotomy after complete initial surgery and two other patients who refused second-look laparotomy and died at 19 and 20 months were considered non-evaluable for tumor response.

*Patient characteristics*

Mean age was 54.9 ± 8.7 yr, with a performance status of 0–1 in 75% of the cases. The histological type most frequently encountered was serous cystadenocarcinoma (60.4%). Pathological grade was 3 in 55.6% of the patients. Fourteen patients were in stage IIIA (29.2%); among them complete macroscopic surgery was performed in only five. Characteristics of the patients are summarized in Table 1.

Therapy toxicity was recorded. Hematological toxicity was defined by anemia requiring transfusions, leukopenia below 1000/mm³ or thrombopenia below 50,000/mm³.

Kaplan-Meier survival curves were calculated from date of pathological diagnosis to death or to January 1984. The log-rank method was used to determine prognostic factors.

*Table 1. Characteristics of patients with stage III and IV ovarian cancer*

| | | % |
|---|---|---|
| No. | 48 | |
| Mean age (yr) | 54.9 ± 8.7 | |
| Performance status | | |
| 0 | 10 | 25 |
| 1 | 20 | 50 |
| 2 | 9 | 22.5 |
| 3 | 1 | 2.5 |
| unknown | 8 | |
| Stage | | |
| IIIA | 14 | 29.2 |
| IIIB | 19 | 39.6 |
| IV | 15 | 31.2 |
| Histological type | | |
| serous | 29 | 60.4 |
| mucinous | 1 | 2.1 |
| endometrial | 3 | 6.2 |
| undifferentiated | 14 | 29.2 |
| clear cell | 1 | 2.1 |
| Histological grade | | |
| 1 | 5 | 13.9 |
| 2 | 11 | 30.6 |
| 3 | 20 | 55.6 |
| unknown | 12 | |
| Mean total tumor volume (cm²) | 257 ± 174 (27 measures) | |
| Mean largest mass volume (cm²) | 162 ± 186 (38 measures) | |
| Initial surgery | | |
| complete | 5 | 10.4 |
| cytoreduction > 50% | 22 | 45.8 |
| biopsy only or cytoreduction < 50% of total tumor volume | 21 | 43.8 |

## RESULTS

*Tumor response*

Ten patients had a complete response (22.7%), nine of the evaluable stage III patients (31%) and

one of the stage IV group (7%). Four stage IIIA and IIIB patients were complete responders. Eight of the stage III patients had surgical cytoreduction of more than 50% and two had only a biopsy at initial surgery. Six had serous carcinoma and four undifferentiated carcinoma.

Partial responses were observed in 13 patients (29.5%): eight of the stage III patients (27.6%), including all of the IIIB group, and five of the stage IV group (33%). An incomplete surgical cytoreduction was performed at the time of diagnosis in only four of these partial responders. Pathology was serous carcinoma in seven patients, undifferentiated in four and endometrial in two.

Stable disease was observed in eight patients (18.2%), six stage III (20.7%) and two stage IV (13.3%). Progressive disease was seen in 13 patients (29.5%), six stage III (20.7%), including two patients who had complete initial surgery, and seven stage IV (47%).

Twenty-six patients died, including 14 stage III and 12 stage IV, 25 of progressive disease. Twenty-two were still alive in January 1984, 12 disease-free, with a median follow-up of 26.5 months (12-50 months), and ten with persistence of the disease, with a median follow-up of 25 months (13-42 months).

Among the five patients whose initial surgery was complete, two remained disease-free and two had recurrent disease at second-look laparotomy; of these, one died at 17 months and the other was alive at 13 months. The last one, who refused the second look, died at 20 months. Tumor responses are summarized in Table 2.

*Survival*

Overall median survival observed was 22 months. Probability of survival was 41% at 2 yr and 33% at 3 yr (Fig. 1). In stage III patients median survival was 25 months, with a survival of 43% at 3 yr. In stage IV disease median survival was 15 months; three deaths occurred in the first month of therapy (one was related to therapy) and one death in the second month.

Among the 23 responders, there were six deaths. Median survival probability of the non-responders was only 11 months. Survival was significantly longer in responders than in non-responders ($P < 0.001$). Median survival was 5 months after the beginning of the second therapy regimen in patients who had residual disease after initial therapy. No response was seen among evaluable patients receiving melphalan or melphalan and hexamethylmelamine.

*Prognostic factors*

Probability of survival appeared to be better when age was below 55 yr, total tumor mass was below 200 $cm^2$, largest single mass was below 100 $cm^2$, histological grading was 1 or 2 and surgical tumor reduction was over 50%, but none of these differences were significant.

No difference appeared between serous carcinoma and other histological types, nor between patients staged IIIA and IIIB.

*Toxicity*

Alopecia, nausea and vomiting occurred in all patients. Other complications were anemia

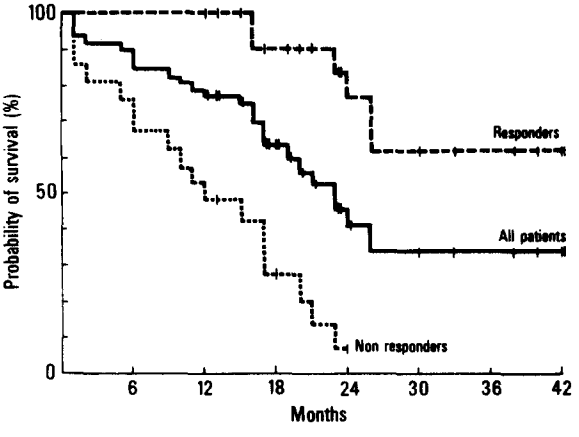


*Fig. 1. Probability of survival for patients with advanced cancer treated with adriamycin and cis-platinum.*

*Table 2. Tumor responses*

| | | Second-look laparatomy | | | | Death before second look |
|---|---|---|---|---|---|---|
| | *n* | CR | PR | SD | PD | |
| NED* after initial surgery | 2 | | | | 2 | |
| IIIA | 9 | 4 | | 3 | 1 | 1 |
| IIIB† | 18 | 5 | 8 | 3 | | 2 |
| IV | 15 | 1 | 5 | 2 | 2 | 5 |
| Total evaluable patients | 44 | 10 (22.7%) | 13 (29.5%) | 8 (18.2%) | 5 | 8 (29.5%) |

*Two patients remained disease-free at second-look laparotomy and one refused.
†One patient refused second-look laparotomy.

requiring transfusions (five patients, 10.4%), leukopenia (seven patients, 14.6%), thrombopenia (one patient, 2.1%), heart failure (three patients, 6.2%), supraventricular arryhthmia (three patients, 6.2%), adriamycin extravasation with cutaneous necrosis (four patients, 8.3%), minor hypersensitivity reactions such as coryza (five patients, 10.4%), buccal ulceration (four patients, 8.3%), transitory renal insufficiency (one patient, 2.1%), dizziness, paresthesias, orthostatic hypotension and xerostomia (one patient each, 2.1%). One therapy-related death occurred, due to septicemia in a leukopenic patient.

Overall, 28 patients (58%) had one or more of these side-effects, excluding alopecia and vomiting, but only four had life-threatening complications (acute heart failure and septicemia). Forty-three patients (89.6%) received the full doses of the two drugs; in the other patients doses had to be reduced.

## DISCUSSION

Median survival of over 20 months in advanced ovarian carcinoma has been reported with Hexa-CAF, ADM-cyclophosphamide and DDP alone or in combination [2, 3, 5, 7, 8, 10]. Median survival of 22 months observed with the ADM-DDP association in this study appears to be one of the best reported results, especially when considering that four patients died in the first 2 months of therapy.

Clinical criteria for therapeutic responses have proven to be too inaccurate [11-14]. Therapeutic responses should be objective responses determined by second-look laparotomy or by evident progression. The objective response rate used in this study is thus not comparable to response rates in most previous studies. Our objective response rate of 52.2% with a median survival of 22 months appears much more realistic than a clinical response rate of 90% with a median survival of only 19 months, as reported in another recent study [15]. Based on these same criteria, the 39 advanced ovarian carcinoma treated between 1975 and 1979 in our institution with chemotherapy regimens not including DDP showed an objective response rate of only 11.5%, with a median survival of 10 months.

Among accepted prognostic factors in advanced ovarian cancer are initial staging and initial cytoreduction, the best results being observed in stage IIIA [14]. In our study the same conclusion can be drawn as for initial staging, but not for the residual disease after initial debulking surgery. However, our number of patients could be insufficient to show a difference in survival.

Toxicity remains important, reflecting side-effects of both drugs used. ADM cardiotoxicity was not exceptional. However, hematological toxicity appeared to be less common with ADM-DDP than in regimens adding cyclophosphamide to ADM-DDP or Hexa-CAF [3, 14].

Nausea and vomiting were the main problems, as previously observed [14].

Improved response rate and survival prolongation are achieved with ADM-DDP in ovarian carcinoma, but cure rate will most likely remain low. Until more effective cytotoxic drugs are found, our results indicate that the following therapeutic approach could be more effective than previous ones: for stage IIIB or IV patients, debulking surgery can be performed after the first chemotherapy courses if they lead to clinical response, and are then followed by additional courses, as described by Parker *et al.*, who reported a median survival of 36 months with such an approach [18].

This study also confirms the first results achieved with the use of ADM-DDP combination in ovarian cancer with an overall survival as good or better than many more complex and more toxic regimens.

**Acknowledgement**—The authors wish to thank Mrs Fecteau and Mavroyannis for their assistance.

## REFERENCES

1. Longo DC, Young RC. The natural history and treatment of ovarian cancer. *Ann Rev Med* 1981, **32**, 475-90.
2. Parker LM, Griffiths T, Yankee RA *et al.* Combination chemotherapy with adriamycin-cyclophosphamide for advanced ovarian carcinoma. *Cancer* 1980, **45**, 669-674.
3. Young RC, Chabner BA, Hubbard SP *et al.* Advanced ovarian carcinoma. A prospective clinical trial of melphalan (L-PAM) versus combination chemotherapy. *N Engl J Med* 1978, **299**, 1261-1266.
4. Vogl SE, Pagano M, Kaplan B. Cyclophosphamide, hexamethylmelamine, adriamycin and diammine-dichloroplatinum CHAD vs melphalan for advanced ovarian cancer randomized prospective trial of the Eastern Cooperative Oncology Group. *Proc ASCO* 1981, **22**, 473.

5. Bruckner HW, Cohen CJ, Goldberg JD *et al.* Improved chemotherapy for ovarian cancer with *cis*-diamminedichloroplatinum and adriamycin. *Cancer* 1981, **47,** 2288-2294.
6. Neijt JP, Ten Bokkel Huinink WW, van den Burg MEL *et al.* Combination chemotherapy with Hexa-CAF and CHAP 5 in advanced ovarian carcinoma. A randomized study of the Netherlands joint study group for ovarian cancer (Abstract C-577). *Proc ASCO* 1983, 148.
7. Griffin JP, Belinson J, Cynn J *et al.* Combination chemotherapy of ovarian carcinoma with CAP. *Proc ASCO* 1981, **22,** 468.
8. Parker CM, Griffiths CT, Janis D *et al.* Advanced ovarian carcinoma: integration of surgical treatment and chemotherapy with cyclophosphamide (C), adriamycin (A) and *cis*-diamine-dichloroplatinum (P) (Abstract C-599). *Proc ASCO* 1983, 153.
9. Bruckner HW, Cohen CJ, Gusberg SG *et al.* Chemotherapy of ovarian cancer with adriamycin and *cis*platinum. *Proc AACR* 1976, **17,** 287.
10. Gershenson DM, Wharton JT, Herson J *et al.* Single-agent *cis*-platinum therapy for advanced ovarian cancer. *Obstet Gynecol* 1981, **58,** 487-496.
11. Smith JP, Delgado G, Rutledge F. Second-look operations in ovarian carcinoma post-chemotherapy. *Cancer* 1976, **38,** 1438-1442.
12. Mangioni C, Bolis G, Molteni P, Belloni C. Indications, advantages and limits of laparoscopy in ovarian carcinoma. *Gynecol Oncol* 1979, **7,** 47-55.
13. Smith JP, Schwartz PE. Second-look laparotomy and prognosis related to extent of residual disease. In: Van Oosterom A, Muggia FM, Cleton FJ, eds. *Therapeutic Progress in Ovarian Cancer, Testicular Cancer and the Sarcomas.* The Hague, Martinus Nijhoff, 1980, 77-94.
14. Williams CJ, Mead B, Arnold A *et al.* Chemotherapy of advanced ovarian carcinoma: initial experience using a platinum-based combination. *Cancer* 1982, **49,** 1778-1783.
15. Williams CJ, Whitehouse JMA. Combination chemotherapy of advanced ovarian carcinoma with *cis*-diamminedichloroplatinum (DDP), adriamycin and cyclophosphamide (PACe). *Proc AACR* 1981, **21,** 136.