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Advanced Ovarian Cancer: Three-Year Results of a 6–8 Month, 2-Drug Cisplatin-Containing Regimen

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Abstract—*Fifty-two patients with advanced (stage III and IV) ovarian cancer were treated with a regimen of cisplatin* (100 mg/m^2 *over* 5 *days) and cyclophosphamide* (600 mg/m^2/*day* 4). *Treatment was repeated every* 3–4 *weeks for* 6–8 *months and followed by second look surgery. The median follow up for this single institution study* (1980–1984) *is* 36 *months. The median progression-free survival (projected) is* 24 *months and the median overall survival (projected) is* 37 *months in this group of patients with unfavorable pretreatment characteristics: median age:* 61, *median performance status (ECOG)* 2, *poorly-differentiated tumors:* 60%, *extensive residual tumors* (> 2 *cm*): 65%. *Pretreatment performance status was the only independent predictor for prolonged survival. Pathologically documented complete responses were observed in* 23% *of all patients and* 43% *of the patients who underwent second-look surgery* (28 *patients). Neurotoxicity from this regimen was substantial: it occurred in* 65% *of cases, was severe in* 17% *and was often not entirely reversible. The results with this intensive* 2-*drug cisplatin-containing regimen compare favorably to other more complex regimens in the literature. It is possible that the 'dose intensity' of* cis-*platinum may be the most important element of current therapeutic regimens in ovarian cancer.*

INTRODUCTION

THE CYTOTOXIC treatment of advanced ovarian cancer has evolved from single alkylating agent chemotherapy to the use of more complex and more effective cisplatin drug regimens [1–6]. There remains, however, much controversy as to which cisplatin combination regimen has the most favorable therapeutic index and what is the optimal dose intensity of cisplatin treatments.

In late 1979 we initiated a trial of a relatively high-dose cisplatin in combination with cyclophosphamide in patients with stage III and IV ovarian cancer referred to the Rita and Stanley H. Kaplan Cancer Center of New York University Medical Center. The primary basis for this trial was the assumption that the dose intensity of cisplatin is a determinant of outcome in patients with ovarian epithelial tumors. This hypothesis is supported by the observation of a dose–response curve for *cis*-platinum in clonogenic assays of human tumors [7] and in clinical trials [8]. We chose to combine cisplatin with cyclophosphamide because of possible synergistic antitumor effects [9] and encouraging preliminary data from other clinical trials combining the 2 drugs with or without other agents. In addition, alkylating agents have always been the mainstay of single agent chemotherapy in this disease. We eliminated other drugs from the regimen, thus trying to maximize the doses of *cis*-platinum and cyclophosphamide given as first-line chemotherapy for advanced ovarian carcinoma. We also hypothesized that reassessment of results by surgical restaging would optimally be carried out after 6 months of treatment since in previous studies maximal responses usually occurred by this time [10].

The objectives of this trial were to determine the efficacy and the toxicity of this intensive 2-drug cisplatin-containing regimen in untreated patients with stage III and IV ovarian cancer.

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PATIENTS AND METHODS

Patient population

Between October 1979 and April 1984, 59 patients with stage III or IV ovarian carcinoma, classified according to the International Federation of Gynecology and Obstetrics (FIGO) were entered into this trial. Requirements for eligibility were (1) histologic confirmation of epithelial ovarian cancer (classification of histologic type as per WHO recommendation) [11], (2) patients were no more than 8 weeks postoperative, (3) no prior radiation or chemotherapy, (4) an ECOG performance status of 3 or better, (5) adequate bone marrow reserve (white blood cell count $\geq 4000/\mu l$, platelet count $\geq 100{,}000/\mu l$), and adequate renal function (BUN ≤ 25 mg/DL and creatinine ≤ 1.5 mg/DL), (6) NYU Medical Center approved informed consent. There were no exclusions for age. Seven patients who did not fulfil these original eligibility requirements (2 patients with prior alkylating agent treatment, 3 with unknown primaries confined to the peritoneal cavity [12], 1 with a second active primary (an endometrial carcinoma), and 1 with initially poor renal function who received half cisplatin dosages) were not included in this analysis. Tumor grading was performed by one pathologist (R.D.) and was based on the architectural pattern: Grade 1 described a tumor consisting virtually of entirely glandular (or papillary) differentiation; Grade 3 described a tumor consisting almost entirely of sheets of malignant cells and Grade 2 represented a combination of these patterns.

Cytoreductive surgery

In all patients an attempt was made to remove as much tumor as possible and the cross-sectional diameter of the largest tumor mass remaining after the operation was recorded as being < 2 cm (no or minimal residual disease), 2–5 cm (extensive residual disease) and > 5 cm (bulky residual disease). Initial surgery was performed by the same team of surgeons at NYU Medical Center in all but 5 patients. In those 5 patients detailed information was obtained regarding surgical procedure and amount of residual disease before starting chemotherapy and histologic slides were reviewed. One patient underwent further debulking surgery and bilateral salpyngo-oophorectomy (BSO) and omentectomy at New York University (NYU) Medical Center 3 weeks after the initial laparotomy which had only consisted of a diagnostic biopsy.

Cytotoxic chemotherapy

Chemotherapy was initiated within 2 weeks after operation in the majority of the patients (71%). In only 6% did cytotoxic treatment start more than 4 weeks (but less than 8 weeks) after primary surgery. Cisplatin was given at a dose of 20 mg/m^2/day intravenously (in 1L D_5 1/3 NS over 2 hr) days 1–5 and cyclophosphamide was given intravenously at a dose of 600 mg/m^2 on day 4. This timing was chosen to postpone combined emetic potential of the drugs in recently-operated patients. This inpatient regimen was repeated every 3–4 weeks for 6–8 cycles of chemotherapy. Before the next course was instituted, the leukocyte count had to be $\geq 3500/\mu L$ and platelets $\geq 100{,}000/\mu l$; if treatment had to be delayed by more than 1 week, the cyclophosphamide dose was reduced by 33%. BUN and creatinine were obtained before the next cycle and on day 3 of each cycle with treatment to be held if BUN ≥ 30 and/or creatinine ≥ 2.0. In case of persistant elevation in serum creatinine within the range of 1.4–1.9 mg/100 ml, the cisplatin dose was reduced by 33%. Antiemetics were given to all patients and most often consisted of Lorazepam, diphenhydramine, prochlormethazine with or without intravenous dexamethazone.

Duration of treatment and evaluation of response

Surgical re-exploration of all patients with no evidence of active ovarian cancer was planned following 6–8 cycles of chemotherapy. In patients with no contraindication of peritoneoscopy, this procedure was recommended before second-look laparotomy. In patients with a positive peritoneoscopy at 6 months, 2 additional cycles of chemotherapy were to be given before second-look laparotomy. Guidelines for second-look laparatomy were similar to those for primary surgery: namely, peritoneal fluid cytology obtained immediately after opening the abdomen, accurate description of the location and size of all residual lesions throughout the peritoneal cavity (both lateral abdominal gutters, cul de sac, dome of bladder, omentum if not previously resected, inferior surface of diaphragm), excision of all involved sites if possible and completion of total abdominal hysterectomy (TAH)–bilateral salpingo-oophorectomy (BSO), omentectomy, if not done before and feasible at low risk. In patients who had a peritoneoscopy followed by a laparotomy, only results of the latter procedure were taken into account for categorization of pathological response. In case no disease was found by peritoneoscopy but the patient refused further surgery, the complete response was called 'pathological complete response by peritoneoscopy'. Since the commonly used clinical response criteria for assessing chemotherapy effectiveness are not easily applicable for patients with ovarian cancer (in this series only 7.7% of the patients had measurable disease and 29% had disease by clinical examination and/or abdominal ultrasound or CT scan at the start of chemotherapy) and furthermore are of limited value in predicting outcome, we emphasized

use of the following measures of clinical response as recommended by Decker *et al.* [1]: (a) *Time to disease progression.* (b) *Duration of survival.* Both time to disease progression and survival were calculated from start of chemotherapy.

Evaluation of toxicity

Patients were considered evaluable for toxicity when adequate information was available for determining the effect of treatment after a minimum of 1 course of chemotherapy with cisplatin and cyclophosphamide. Patients in whom the treatment schedule was modified at some point in the treatment course were not excluded from the analysis but were indicated as in Tables describing toxic effects of therapy (Tables 4–6).

'Salvage therapy'

The suggested 'salvage' regimen for patients with progressive disease, persistent tumor at second-look laparotomy or relapse was the combination of hexamethylmelamine (150 mg/m^2/day p.o., d 1–10) and 5-fluorouracil (450 mg/m^2 i.v. daily × 4). However, since this reigmen required oral administration and was potentially neurotoxic only 11 patients received it while the others received a number of other second-line therapies which included single agents such as doxorubicin, melphalan, carboplatin, deoxydoxorubicin, intraperitoneal therapy with cisplatin or Ara-C, combinations (cytoxan–methotrexate–5-fluorouracil) or radiotherapy (alone or combined with cisplatin).

Statistical analysis

Life-table analysis was used to evaluate survival time and time to progression. All 52 eligible patients were included. Cases withdrawn from the study not because of progression (i.e. because of early toxicity or because of inappropriate 'consolidation' chemotherapy with hexamethylmelamine and 5-fluorouracil) were included in the life-table analysis in 2 alternate ways: one using their real survival times and real times to progression and the other regarding them as censored observations from the day the 'consolidation' therapy was given. The overall survival and time to progression curves were computed both ways. Analysis of subsets of patients grouped according to levels of a prognostic factor was done using the latter method, censoring the patients from the day they went off-study. To adjust the life-table analysis of a particular prognostic factor, e.g. extent of residual disease, for the effects of another prognostic factor, e.g. performance status, a stratified approach was used in which adjusted differences in survival (or time to progression) patterns were assessed by the Cox–Mantel method [13, 14]. Cox regression analysis was used to confirm the results of the stratified life-table approach.

Statistical tests were considered significant at the P 0.05 level. Unless otherwise noted, all significance levels were derived from the log-rank test [15].

RESULTS

Study population

Characteristics of the 52 eligible patients are outlined in Table 1. It should be pointed out that 5 of the 46 patients classified as Stage III disease might have been of more advanced stage since pleural effusions were present but did not have attempts at confirming cytology.

Second-look surgery

Among the 52 patients, 28 underwent surgical re-exploration for assessing tumor response (Table 2). Seventeen patients started chemotherapy with bulky residual disease ($\geq$ 2 cm) and 11 with non-bulky residual disease ($<$ 2 cm). Three were found to have progressive disease (all by laparotomy), 13 incomplete tumor regression (peritoneoscopy 2, laparotomy 8, laparotomy preceeded by a negative peritoneoscopy 3) and 12 pathologically documented complete tumor regression (CR) (peritoneoscopy alone 3, laparotomy with a prior positive peritoneoscopy 2, laparotomy with a prior negative peritoneoscopy 3, laparotomy alone 4). The 3 patients with a negative peritoneoscopy alone refused further surgical re-exploration. The median time between onset of chemotherapy and second-look surgery was 6 months for peritoneoscopy and 8 months for laparotomy.

Among the patients with a pathological 'CR', 5 had residual disease at initial laparotomy $>$ 2 cm and 8 had poorly-differentiated tumors. Three relapses have occurred (2 in patients with initial disease $<$ 2 cm, 1 in a patient with initial bulky disease) with a median case follow-up of 50 months (range 26–61). Two of these relapsing patients have died 29 and 48 months from start of therapy.

The reasons why second-look surgery was not performed in 24 patients are outlined in Table 2. Nine patients still had clinical evidence of active ovarian cancer after a 6–8 months treatment period. Four experienced early treatment-related toxicity among whom 1 died and 3 were switched to other induction regimens, 3 were considered as having surgical contraindications to second-look and 8 refused re-exploration. The median age of the patients not having surgical re-exploration was 64 years (range 45–81) compared to 51 years (range 22–78) for those undergoing surgical re-exploration.

Time to disease progression and overall survival

With a median case follow-up time of 36 months

Table 1. Patient characteristics

Number	Minimal post op residual disease (< 2 cm) (n = 18) Number	Bulky post op residual disease (≥ 2 cm) (n = 34) Number	Total (n = 52) No.	%
Age				
< 60	6	19	25	48
≥ 60	12	15	27	52
Performance status				
0–1	13	13	26	50
2–3	5	21	26	50
Stage				
III	15	31	46	88.5
IV	3	3	6	11.5
Type of surgery				
TAH–BSO–omentectomy	16	9	25	48.1
Incomplete surgery	2	20	22	42.3
Biopsy only	0	5	5	9.6
Histologic grade				
Well-differentiated	2	5	7	13.5
Moderately well-differentiated	4	10	14	26.9
Poorly-differentiated	12	19	31	59.6
Histologic type				
Serous	9	24	3	63.5
Undifferentiated	4	7	11	21.2
Endometrioid	2	2	4	7.7
Mucinous	2	1	3	5.8
Clear cell	1	0	1	1.9

Table 2. Second-look surgery

Patients with second-look surgery (n = 28)	
Progression of disease	3
Incomplete tumor regression	13
Macroscopic residual disease	4
Microscopic residual disease	9
Complete tumor regression	12
by peritoneoscopy alone	3
by laparotomy	9
Patients with no second-look surgery (n = 24)	
Unexplored persistant disease	9
Early treatment discontinuation	4
Contraindications to second-look surgery	3
Refused re-exploration	8

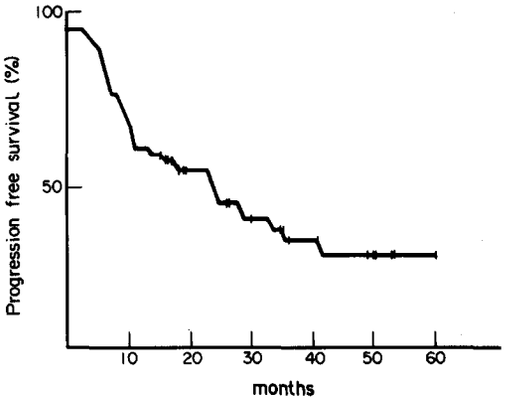

Fig. 1. Progression-free survival curve.

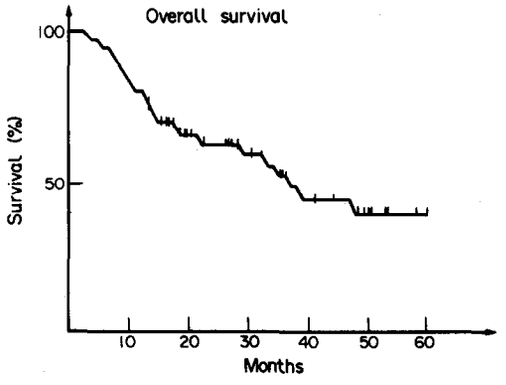

Fig. 2. Overall survival curve.

on all patients (range 15–66 months), 30 patients have progressed (22 in the bulky disease group), 24 have died (20 in the bulky disease group). Twenty-eight are alive, 22 with no evidence of disease and 6 with active disease. All 52 patients are included in the progression-free survival and overall survival curves illustrated in Figs 1 and 2. The median time to disease progression (projected) is 24 months and the median survival time (projected) is 37 months. As noted in the statistical section, further comment is required on 6 patients entered in this trial. In 4 patients the initial cisplatin–cyclophosphamide

Table 3. Median survival in months by entry characteristics

	No. of patients	Median survival (months)
Age < 60	25	47
Age ≥ 60	27	Not reached (> 60)
PS = 0,1	26	Not reached (> 60) P=0.003*
PS = 2,3	26	18
Residual tumor < 2 cm	18	Not reached (> 60) P=0.02†
Residual tumor ≥ 2 cm	34	21
Well-differentiated tumor	7	Not reached (> 53)
Moderately well-differentiated tumor	14	28
Poorly-differentiated tumor	31	47

*When adjusted for residual disease $P < 0.03$.
†When adjusted for performance status P non-significant.

therapy was changed after 1–3 cycles of therapy because of early neurotoxicity or nephrotoxicity. They were subsequently treated with other regimens: cyclophosphamide–doxorubicin (1), cisplatin–doxorubicin (1) and hexamethylmelamine–5-fluorouracil with or without cyclophosphamide (2). In 2 additional patients who refused surgical re-exploration after a full 6 cycles of protocol treatment, a 'consolidation' regimen with hexamethylmelamine and 5-fluorouracil was given. If these 6 patients with protocol violations or early cisplatin discontinuation are censored at the time they were started on another treatment, the projected median survival of the entire patient population is 48 months.

The sites of progressive disease, among 30 patients were: pelvic mass (16 = 53%), abdominal mass (14 = 47%), malignant ascites (18 = 60%), malignant pleural effusion (3 = 10%), retroperitoneal and/or supraclavicular nodes (5 = 17%), liver (2 = 7%), brain (1 = 3%).

Several patient characteristics have been studied for possible effect on survival within our patient population. As shown in Table 3, performance status (PS) (Eastern Cooperative Oncology Group) and residual tumor bulk at the time of initiation of chemotherapy were found to have an impact on survival: patients with PS 0–1 did better (P = 0.003) than patients with PS 2–3 and patients with no or minimal residual disease following the initial surgery did better (P = 0.02) than patients with extensive or bulky disease (≥ 2 cm) (Fig. 3). After adjusting for performance status, however, size of residual tumor bulk was not associated with survival. On the other hand, performance status was an independent prognostic factor, retaining its statistical significance (P = 0.03) after adjusting for residual disease. Age and degree of tumor differentiation did not significantly affect survival in this trial. These findings were confirmed by the Cox regression analysis.

Toxicity

All patients were included in toxicity analysis since they all had follow-up on at least 1 course of cisplatin and cyclophosphamide. Eventual modifications of treatment schedule were made in 6 patients because they were unwilling to adhere to the 5-day schedule. In one of these patients continued intolerance to cisplatin led to premature interruption of the regimen after 2 cycles and substitution of doxorubicin for cisplatin. The 5 other patients did receive a full induction treatment with the combination of *cis*-platinum and cyclophosphamide (median cumulative dose of cisplatin 480 mg/m^2, range 30–720 mg/m^2).

The major toxicity of this combination chemotherapy regimen was neurotoxicity which developed in 65% of this patient population (34 patients) and was disabling in 17% (ECOG grade 3: 9 patients, 2 of whom had a fracture of the ankle attributed to a severe loss of proprioception). Onset of paresthesias occurred after a median of 4 courses with a range from 2 to 8. Among the 25 patients with cisplatin-induced neurotoxicity who did not get other neurotoxic drugs as 'salvage' therapy and did not die prematurely, only 5 experienced complete reversibility of the neurotoxic effects. In the remaining 20, some improvement over time was noted. Although there was a trend for patients who received higher cumulative doses of platinum to have more severe neurotoxicity, dosages as high as 800 mg/m^2 could be non toxic while dosages of 320 mg/m^2 could result in grade 3 toxicity. The median age of the patients with and without neurotoxicity was 60 (range 42–81) and 54 (range 22–78) respectively.

Nephrotoxicity was analyzed by looking at the changes in serum creatinine over the pretreatment value. Five patients who experienced no or mild renal toxicity (defined as a rise in serum creatinine that is less or equal to 1.25 times the pretreatment value) had a median age of 48 (with a range of 47–73), all of whom also had neurotoxicity which

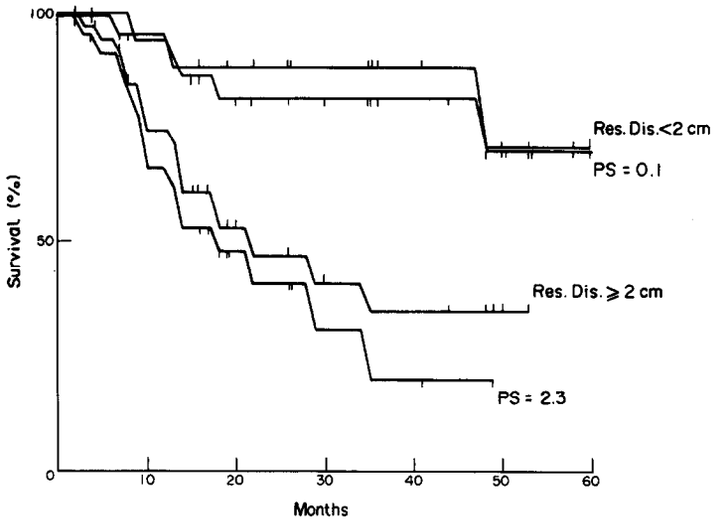

Fig. 3. Overall survival curves according to performance status and postoperative residual disease.

Table 4. Hematologic toxicity of cisplatin-cyclophosphamide therapy

	No. of patients		%
White cell count suppression			
≥ 4000	3	[1]	5.8
2000–3999	31 (3)		59.6
< 2000	17 (3)	[1]	32.7
Unknown*	1		1.9
Platelet count suppression			
≥ 100,000	31 (4)	[1]	59.6
50–99,999	12 (2)	[1]	23.1
25–49,999	6		11.6
< 25,000	2		3.8
Unknown*	1		1.9
Required RBC transfusion	29 (3)		55.8

( ) No. of patients who were switched to a different treatment schedule (day 1 or day 1+8 instead of day 1–5) for cisplatin administration.

[ ] No. of patients who got only 1 course of cisplatin and cyclophosphamide.

* Hospital chart of this patient not accessible.

was severe in 1 (ECOG Grade 3). The median age of the 39 patients who experienced moderate nephrotoxicity (or a rise in serum creatinine that exceeds 1.26–2.5 times the pretreatment value) was 61 (range 22–81) and 26 of them had neurotoxicity. Among the 8 patients who had severe nephrotoxicity (or a rise in serum creatinine 2.6–5 times the pretreatment value) the median age was 52 (range 43–70) and 3 had neurotoxicity.

The lowest WBC and platelet counts recorded during induction therapy with cisplatin and cyclophosphamide are shown in Table 4. Only 5 patients had WBC counts below 1000 and 1 of them died from a septic shock [this patient also had severe thrombocytopenia (6000) and renal failure]. The median lowest recorded WBC count was 2240 with a range of 25–6800 and the median lowest recorded platelet count was 118,000 with a range from 6000 to 506,000 in 51 evaluable patients. Fifty per cent of the patients reached their lowest recorded WBC within the 2 first treatment courses and their lowest recorded platelet count within the 3 first treatment cycles. The incidence of anemia was substantial: 55.8% of the patients required RBC transfusion. The median lowest hemoglobin value was 8.5 mg/100 ml (range 6.5–11.6) and the median lowest hematocrit value was 25.4% (range 19–35%). One patient experienced a severe hemolytic anemia following her first course of therapy. However, this recurred when she was later retreated with a non-platinum-containing regimen. Nausea and vomiting were universal and severe (ECOG Grade 3) in 36.5% of the patients (19 patients). Gastrointestinal intolerance led to premature discontinuation of cisplatin in only 2 patients. As shown in Table 5, treatment modifications were frequently required because of the occurrence of toxicity. In 46% of the patients the doses of cisplatin were reduced and in 44% of the patients therapy with cisplatin had to be discontinued before the completion of the 6 planned courses of chemotherapy. Neuro- and/or nephrotoxicity accounted for most of these alterations in treatment plan (Table 5). The median cumulative dose of cisplatin given to the entire patient population was 479 mg/m^2 (range 100–800) and the median cumulative dose of cyclophosphamide given was 3600 mg/m^2 (range 600–6700).

DISCUSSION

The projected median survival of 37 months in this group of 52 patients with advanced ovarian cancer is one of the highest recorded among plati-

Table 5. Toxicity-related treatment modification

Type of treatment modification*	No. of toxic patients with treatment modification					Total	
	Neuro-toxicity	Nephro-toxicity	Neuro- + nephro-toxicity	Hematol-logic toxicity	G.I. toxicity	No. (n=52)	%
Cycle(s) delayed	—	2	—	15	—	17	32.6
Reduced CTX doses	—	—	—	15 (4)	—	15	28.8
Reduced DDP doses	6	6 (1)	4 (1)	6 (3)	2	24	46.1
DDP discontinued (CTX continued)	7 (1)	7	3	—	1 (1)	18	34.6
CTX discontinued†	—	—	—	1	—	1	1.9
DDP and CTX discontinued†	—	2	1	1	1	5	9.6

( ) No. of patients switched to a different treatment schedule of cisplatin (DDP) administration.
* Recorded in this Table only if occurred before the completion of 6 cycles of therapy.
† See text for further details.

num containing regimens. Excluding patients with protocol violation of early termination of *cis*-platinum does not select out patients with an unfavorable prognosis (median survival time 37 months vs. 48 months for group minus censored patients). With a median case follow-up of 3 years (range 15+ months to 5.5 years) and 24/52 (46%) observed deaths, the median survival should be accurately estimated by the Kaplan–Meier curve. Much uncertainty, however, exists, as far as impact of this regimen on long-term survival. The surgical re-exploration rate of 54% in this trial is comparable to that of most other published chemotherapy trials in advanced ovarian cancer [1, 4, 5, 6]. Since the overall pathologically-defined complete response rate is only 23%, our long-term survival may eventually not be higher than in other series. In addition, a continued pattern of relapses may be expected as noted by others [16]. Only a longer follow-up will determine if this 2-drug regimen is associated with a definable cure rate. Up to now, 9 patients in our study have lived more than 4 years following diagnosis (range 44–58 months) and 7 have been relapse-free. Among these 7 patients, 4 had no or minimal residual disease (< 2 cm) and 3 had extensive residual disease (≥ 2 cm), 4 had well- or moderately well-differentiated tumors and 3 had poorly-differentiated tumors. All 7 patients but 1 had an ECOG performance status of 0 or 1 and all but 2 had a negative second-look operation. This result appears similar, so far, to one report on 59 stage III/IV ovarian cancer patients treated with a brief (6 months) intensive course of a 4-drug platinum-containing regimen (H-CAP or hexamethylmelamine, cyclophosphamide, adriamycin and cisplatin) [6]. Twenty-six per cent of those patients were alive and disease-free at a minimum follow-up of 44 months and a maximum follow-up of 70 months. In this group of patients the pathologically documented complete response rate was comparable to ours (23%).

Survival is undoubtedly the single most important parameter of treatment efficacy in ovarian cancer: assessment of response is notoriously difficult and progression-free survival is a function of the quality of patient's follow-up. The long interval (13 months) between the median progression-free survival time and the median overall survival time observed in this study is noteworthy. We attribute this to close follow-up and early determination of disease progression and not to the efficacy of second line therapy. Nevertheless, 2 long-lasting (2+ years) complete responses occurred in our relapsing patients: 1 to intraperitoneal Ara-C and 1 to pelvic radiotherapy. Of interest is the finding that performance status at the start of chemotherapy was the only independent prognostic factor with a significant impact on overall survival in our patient population. In patients with an initial performance status of 0–1, the median survival has not yet been reached and is in excess of 5 years. The Netherlands Joint Study Group for ovarian cancer also found that performance status was the most important prognostic factor for survival in their randomized trial of CP (cyclophosphamide, cisplatin) vs. $CHAP_V$ (cyclophosphamide, hexamethylmelamine, adriamycin and cisplatin) (ASCO, 1985, oral presentation of Abstract C-442).

Comparison between this single institution trial and other trials of cisplatin based chemotherapy in advanced ovarian cancer requires all the caveats of analysis outside the context of randomized studies. Our patient population did have the usually described poor pretreatment characteristics with 1 possible exception: while more than 80% of our patients had big bulky disease (> 5 cm) before surgery, only 23% were left with tumor masses greater than 5 cm after surgery and—as a result—only 37% had disease measurable or evaluable at the start of chemotherapy. Although this is similar to the Mayo Clinic experience in which 28% of the patients start cyclophosphamide + cisplatin

Table 6. Platinum (PT) and an alkylating agent as initial therapy for stage III–IV ovarian cancer

Institution (Ref)†	Patient dose/ cycle (mg/m^2)	Intended treatment period	% patients with Residual tumor > 2 cm	% patients with High grade tumor	Total No. patients	Median survival (months)
Mayo Clinic	50	1 year	52	57	21	40 m
Milan (GICOG)*	50	6–12 m	72	38	128	19 m
Sydney*	50	1 year	64	100	17	18 m
Mayo Clinic	60	1 year	44	40	89	24 m
M.D. Anderson	60	1 year	56	54	82	30 m
Netherlands*	75	6–9 m	NA	NA	100	26 m
New York University	100	6–8 m	65	60	52	37 m
National Cancer Institute	200	3–4 m	56	38	24	too early

*Multicenter Randomized Studies.
†References are in order [1], [19], [20], [21], [22], [23], [24].
NA = not available.

therapy with tumor masses greater than 5 cm [1], many other trials of cisplatin combination chemotherapy in Stage III and IV ovarian cancer report on at least 50% of the patients having tumor masses greater than 5 cm at the start of drug therapy [4, 17, 18]. We think that this discrepancy most likely reflects the surgical aggressiveness of the gynecological team at our Institution. Alternatively, it could represent some self-selection process on the part of patients allowing them to present with more 'debulkable' disease. It should be emphasized, however, that no patient was excluded from this study because of big bulky residual disease. With these reservations in mind and given the overall poor prognostic features of our patient population, we feel that comparing published trials of cisplatin combination chemotherapy to ours may still shed some light on 3 current controversial issues: (1) the optimal number of drugs in the first line chemotherapy for Stage III–IV ovarian cancer [2, 3]; (2) the possible benefit from adding doxorubicin to cisplatin and an alkylating agent, (3) the effect of cisplatin dose-intensity.

Among the most relevant studies reporting on a 2-drug combination regimen with cisplatin and an alkylating agent in advanced ovarian cancer the median survival has ranged from 18 months to 40 months [1, 19, 20, 21, 22, 23, 24]. As shown in Table 6, cisplatin doses ranged from 50 mg/m^2 to 200 mg/m^2/cycle and the intended treatment period from 3 months to 1 year. The first Mayo Clinic study randomizing cisplatin + cyclophosphamide (CP) vs. cyclophosphamide alone [1] was interrupted early because of the clear superiority of the 2-drug regimen with only 21 patients enrolled in the CP arm. When they later randomized a similar 2-drug regimen using a slightly higher cisplatin dose with a 4-drug regimen containing hexamethylmelamine, cyclophosphamide, adriamycin and cisplatin, the median survival was found to be 24 months as opposed to 40 months even though the patients had the initial favorable characteristics of good performance status (median of 1-ECOG), 56% debulked to less than 2 cm cross-sectional diameter for the largest residual lesion and 40% with poorly-differentiated tumors [21]. It appears from Table 6 that all regimens utilizing cisplatin dosages of at least 60 mg/m^2 can achieve a reproducible median survival in excess of 2 years. It will be of interest to see whether the ongoing NCI trial using an ultra-high cisplatin dosage over a short period of time [24] will lead to markedly improved results and whether any of the above mentioned studies will report on long-term disease-free survivors. This high level of cisplatin dose-intensity, however, may produce accelerated and more severe neurotoxicity [24].

The importance of the dose-intensity of cisplatin in the first line chemotherapy treatment for advanced ovarian cancer clearly remains a controversial issue. The good results of our study support the hypothesis of a dose–response relationship for cisplatin which, however, can only be clinically validated by randomized trials. At the University of Indiana, the toxic 3-drug regimen PAC (cisplatin, doxorubicin and cyclophosphamide) did not prove to be superior when the cisplatin dose per cycle (20 mg/m^2/day × 5 days) was used rather than the lower dose (50 mg/m^2 in 1 day) but cisplatin treatment was stopped in all patients at a cumulative dose of 300 mg/m^2 [27]. In a large randomized study including more than 250 women with measurable or evaluable metastatic epithelial ovarian cancer, the Eastern Cooperative Oncology Group was unable to demonstrate a dose–response relationship for cisplatin given either at a dosage of 37.5 or 75 mg/m^2 q 3 weeks in the subset of patients without prior chemotherapy (= 52% of the patients) [28]. All these patients had residual tumor < 2 cm. Median survival of the entire population (including patients pretreated with alkylating agent and radiotherapy) was 14 months with no difference between

the 2 cisplatin–hexamethylmelamine regimens. It is unclear at the present time whether enough untreated patients were entered into this trial to provide a satisfactory confidence interval to this observation. Two recent pieces of data still leave very much open the possibility that the dose-intensity of *cis*-platinum may be unimportant. Ozols *et al.* recently provided evidence for a dose–response relationship for cisplatin in ovarian cancer: they treated patients refractory to conventional doses of cisplatin with ultra-high doses of 200 mg/m^2/cycle and noted a 32% objective response rate as well as improved survival [25]. Ten Bokkel Huinink *et al.* reported pathological complete remissions in 9 of 27 patients treated with high-dose platinum given as intraperitoneal dialysis therapy. All of these patients had received prior intravenous cisplatinum-based therapy at conventional doses and had residual disease (< 2 cm) at the time of restaging laparotomy just before intraperitoneal catheter placement [26]. Potential advantages of currently available aggressive regimens may not apply to all groups. While patients with bulk disease do react poorly in most series advantage may be limited to patients with small bulk disease, e.g. those acceptable for intraperitoneal therapy. Such patients may be the ones who would experience a real improvement in cure rate with cisplatin dose escalation. In our study, 70% of the patients with initial postoperative disease < 2 cm are alive at 4 years (Fig. 3) but a longer follow-up is necessary to be sure that a plateau has been reached in their survival curve.

Focus on 3- or 4-drug cisplatin-containing regimens, as compared to 2-drug cisplatin-containing regimens reveals conflicting observations. In the randomized trials comparing CP (cyclophosphamide and cisplatin) to CAP (cyclophosphamide, doxorubicin, and cisplatin) superiority of the 3-drug regimen has been found by some investigators [29, 30] but not by others [19]. It should be emphasized that in all those trials, doxorubicin has simply been added to standard doses of cisplatin (50 or 60 mg/m^2/cycle) and an alkylating agent with no effort at maximizing the doses of these agents in the 2-drug regimen which, as a result, has been less toxic than the 3-drug regimen. One cannot state if the putative superiority of the 3-drug regimen would hold up if equitoxicity had been achieved. On the other hand, the 2-drug regimen CP (cyclophosphamide and cisplatin) compared to CHAP (cyclophosphamide, hexamethylmelamine, adriamycin and cisplatin) in the 2 large randomized studies of the Mayo Clinic and the Netherlands [21, 23] yielded equivalent results as far as progression-free survival and overall survival are concerned. For this reason, the 2-drug regimen cisplatin and cyclophosphamide is increasingly being considered as a 'standard' chemotherapeutic treatment to which new regimens should be compared. It is important, however, to keep in mind that there are presently no data showing a long-term survival advantage for combination chemotherapy. Several investigators have shown combination therapy with or without *cis*-platinum to be superior to therapy with alkylating agents. This has not, however, been demonstrated comparing combination regimens to *cis*-platinum alone, especially when it is given aggressively. In fact, early results from Mangioni *et al.* [19] in a trial of over 400 women has failed to show any survival advantage of PAC vs. cytoxan/platinum vs. platinum as a single agent. *Cis*-platinum was given at conventional doses (50 mg/m^2) in all arms.

Toxicity of all cisplatin-containing regimens is substantial. There was a high incidence (65%) of neuropathy experienced by our patients, which might be in part related to our high cisplatin dose per cycle (100 mg/m^2). In an elegant prospective study on cisplatin-induced neuropathy in ovarian cancer patients considerable concentrations of platinum were found in various tissues from 4 patients as long as 4 months after treatment with cisplatin, with the highest levels recorded in residual tumor, dorsal root ganglia and the median and sural nerves [31]. It would be of interest to further define whether or not the schedule of cisplatin administration might influence the incidence and the severity of cisplatin-related neurotoxic effects, and under which circumstances the neuropathy is reversible. We could not find a correlation between the development of renal- and neurotoxicity; this could be explained by the fact that cisplatin doses were systemically reduced in case renal toxicity became apparent, thus protecting these patients from further neurotoxic effects of the drug. Current development of new cisplatin analogs with less or no neurotoxicity and possibly equal activity against ovarian cancer might, however, not only provide means to continue treatment safely in the presence of neuropathy but also eventually replace cisplatin in many, if not all, circumstances [32].

Nephrotoxicity of this cisplatin regimen given over 5 days seemed to be acceptable: only 2 patients, both in their seventies, were switched to other induction chemotherapy regimens after having experienced early but reversible nephrotoxicity. The close monitoring of serum creatinine values in this study (3–4 times a month in most patients) together with the mild hydration program of 1 l/day might explain why only 10% of our patients had no nephrotoxicity as compared to 41% for the $CHAP_V$ regimen in the Dutch study [4]. All our patients reported as having had a moderate to severe nephrotoxicity (see prior definitions) experienced

rapid reversibility of this side-effect except for one who died from a septic shock in a setting of severe neutropenia and thrombocytopenia. She was the only toxic death from this regimen which, overall, led to only mild to moderate hematologic toxicity probably related to the modest dose of cyclophosphamide used.

Enthusiasm for our relatively high-dose cisplatin regimen must be tempered by the substantial toxicity encountered, which precluded administration of a total of 600 mg/m^2 of cisplatin in 44% of our patients. The median cumulative cisplatin dose given in this trial was nearly 500 mg/m^2 and dose reductions because of renal or neurotoxicity were generally required during the fifth course. One might raise the possibility that even shorter periods of intensive therapy (3–4 months) might be equally effective and less toxic. Indeed, survival in this trial was not statistically significantly different in patients who received less than the median cumulative cisplatin dose compared to those who received more.

We reach the following conclusions: (1) this moderately intensive regimen of cisplatin and cyclophosphamide given over 6–8 months to 52 previously untreated Stage III–IV ovarian cancer patients yields a median survival (projected) of 37 months in spite of poor pretreatment characteristics; (2) the true contribution of this regimen to the 5-year survival rate requires a longer follow-up; (3) toxicity is substantial and consists principally of neurotoxicity which has been disabling in almost 20% of the patients.

We feel that further juggling of the known active agents in ovarian cancer in equivalent dosages is unlikely to lead to a major therapeutic breakthrough. A search for new drugs or novel ways of improving the therapeutic index of existing drugs (e.g. intraperitoneal chemotherapy) should be sought. We have embarked on a trial of first line combined modality therapy with surgery, systemic chemotherapy and timed local intraperitoneal cisplatin in advanced ovarian cancer.

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