Tandem High-Dose Chemotherapy with Ifosfamide, Carboplatin, and Teniposide with Autologous Bone Marrow Transplantation for the Treatment of Poor Prognosis Common Epithelial Ovarian Carcinoma

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Presented in part at the 7th European Conference on Clinical Oncology Jerusalem, Israel, November 1993.

Supported by the Amis du Centre des Tumeurs de Tenon and by the Association Pour la Recherche En Cancérologie.

The authors thank the nurses of the Bone Marrow Transplant Unit for the excellent care given to their patients, Dr. L. Chauveinc for the statistics, L. Hughes for editorial assistance, and Pr. A. De Gramont.

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Received November 8, 1995; revision received February 9, 1996; accepted March 11, 1996.

BACKGROUND. A Phase I or II trial was conducted to assess the toxicity and the efficacy of a tandem high dose chemotherapy combining ifosfamide, carboplatin, and teniposide in patients with poor prognosis ovarian carcinoma.

METHODS. Thirty-seven patients were scheduled to receive tandem high dose therapy combining ifosfamide 7500 to 11250 mg/m^2, carboplatin 875 to 1000 mg/m^2 and teniposide 750 to 1000 mg/m^2, followed by autologous bone marrow transplantation (ABMT). Eight patients were refractory to the platin-based regimen, 7 were treated in chemosensitive relapse, and 22 in partial or complete response (PR/CR) were treated. Sixty-six cycles were administered. Sixteen patients were evaluated for response.

RESULTS. The overall response rate was 56% (CR rate: 12%). Toxic effects consisted of mainly renal toxicity, esophagitis, and enterocolitis. Three patients died of therapy-related complications. Since the time of ABMT, the median overall survival (OS) duration of the whole population was 18 months and the survival rate was 14% at 60 months. For the 22 patients treated after PR or CR, the median OS duration was 24 months and the survival rate was 32% at 60 months. Tandem high dose therapy with ABMT was unable to circumvent resistance to conventional chemotherapy or to prolong the duration of survival for patients treated in chemosensitive relapse. For patients treated after CR or PR, the survival results were similar to that achieved with conventional therapy.

CONCLUSIONS. Prospective, randomized studies, including patients only after CR or with minimal residual disease, are urgently required to evaluate the activity of high dose therapy in the treatment of advanced ovarian carcinoma. ***Cancer* 1996; 77:2550–9.** © *American Cancer Society.*

KEYWORDS: ovarian carcinoma, high dose chemotherapy, carboplatin, autologous stem cell transplantation.

Cancer of the ovary is one of the most frequent cancers among females, with about 1 in 70 developing an ovarian carcinoma during her lifetime. Approximately 70% of patients present with advanced stage disease at diagnosis. Substantial improvements have been made in the therapeutic approach of advanced poor-prognosis ovarian carcinoma: about 50% of patients will achieve a clinical complete response (CR) but up to 80% of the patients die of their disease with a survival rate of less than 20% at 5 years.[1–4] Important prognostic variables include International Federation of Gynecology and Obstetrics (FIGO) stage, postsurgical tumor residuum, histologic subtypes, tumor grading, and the age of patients at diagnosis. Residual disease and tumor grade are the most important variables for outcome, fol-

lowed by stage and histologic subtype.[1,2,5-7] Patients with minimal or no macroscopic residual disease after initial debulking surgery have a good chance of disease eradication by postoperative cisplatin (CP)- or carboplatin-based chemotherapy and the highest probability to be long term survivors.[8,9] Recently the combination of taxol and CP has been considered to be superior in terms of survival and progression free survival compared with the standard first line therapy using cyclophosphamide (CPM) and CP.[10] For patients who relapse, if some reports have shown a benefit from secondary debulking surgery, and if some new drugs (mainly taxol) are now available, less than 10 to 20% of these patients can hope to be alive and well at 2 years.[11-14] Whole abdominal irradiation has failed to improve the survival of poor-prognosis ovarian carcinoma.[15] Over the past decade, much has been learned about the potential clinical utility of intraperitoneal chemotherapy that allows us to attain higher intraperitoneal concentrations of drugs than that rendered possible by systemic administration of chemotherapy.[16,17]

To avoid relapses in this particularly chemosensitive tumor after initial surgery and chemotherapy, alternate methods of treatment are clearly needed to prolong the duration of CRs with the aim to increase the 5-year survival rate. One of these therapeutic approaches is based on the concept of dose intensification.[18,19] Autologous bone marrow transplantation (ABMT) allows us to use very high doses of chemotherapeutic agents for the treatment of poor prognosis solid tumors and lymphomas.[19-21] In 1987, we initiated Phase I and II trials of tandem high dose therapy combining ifosfamide (IFM) and carboplatin (CBDCA) with etoposide. (VP-16) or teniposide (VM-26) for adult patients with solid tumors with the aim of defining the response rates and the maximum tolerated doses of these 4 drugs used in combination therapy. In this trial published in 1991, 18 patients with germ cell tumors (GCTs) or gestational metastatic trophoblastic disease received VP-16, IFM, and CBDCA (ICE regimen) and 22 patients with ovarian carcinoma received VM-26 combined with IFM and CBDCA (ICT regimen).[22] The dose response relationship and the spectrum of the extrahematopoietic toxic side effects of these drugs given in high doses makes them suitable for combination therapy and some trials are now available with the ICE regimen given at various levels of doses for the treatment of GCTs and lymphomas.[21-23] For the treatment of ovarian carcinomas, VM-26 has been chosen in our first trial instead of VP-16 because the response rates of this tumor were considered to be 40% for VM-26 and 10% for VP-16 and pharmacologic data of VM-26 used in high doses were well known.[24-26] Moreover, IFM and CBDCA given in high doses have shown antitumoral activity in refractory ovarian carcinomas.[27-34] For all these reasons, we have decided in 1987 to combine VM-26, IFM, and CBDCA for the treatment of advanced poor-prognosis ovarian carcinomas, and we can now report herein the results of an extended trial of this tandem high dose chemotherapy administered to 37 poor-prognosis advanced ovarian carcinoma patients, including the 22 patients of the initial trial.

MATERIALS AND METHODS

Patient Selection and Characteristics

The study was performed in a single institution during an 8-year period between March 1987 and 1995. The treatment was designed for patients with advanced poor-prognosis common epithelial ovarian carcinoma. The patients were scheduled to receive 2 consecutive high dose cycles of chemotherapy. Thirty-seven patients were included in the study. Of these, 32 had FIGO Stage IIIc partially resected ovarian carcinoma and 5 had FIGO Stage IV ovarian carcinoma (3 had histologically proven pleural dissemination and 2 had left supraclavicular node dissemination).[35] Eligibility requirements included the following criteria: age less than 65 years, creatinine clearance $\geq$ 60 mL per minute, hepatic and cardiorespiratory function within normal limits, absence of infection, and absence of detectable bone marrow metastases.

The characteristics of patients are summarized in Table 1. All patients had previously been given a CP-based regimen including doxorubicin and CPM. Performance status was graded according to the Eastern Cooperative Oncology Group (ECOG) criteria as follows: 0 to 1 for 29 patients, 2 for 7 patients, and 3 for 1 patient.[36]

Three categories of patients were defined at the time of ABMT, according to their previous treatment: Group A was composed of 8 patients who were refractory to standard first line (n = 4) or second line (n = 4) CP-based therapy, Group B was composed of 7 patients who were treated in chemosensitive relapse: they were in clinical PR at the time of ABMT after second line CP- or CBDCA-based regimen. Finally, 22 patients (Group C) were treated during partial response (PR) (6 patients) or CR (16 patients) after 6 courses of conventional CDDP-based, first line chemotherapy (doxorubicin-CPM-CDDP) and second-look surgery.

At the time of ABMT, 21 patients had macroscopic residual disease: 9 (6 from Group A, 3 from Group B) had tumor masses > 2 cm in greatest dimension, and 12 (2 from Group A, 4 from Group B, 6 from Group C) had tumor masses $\leq$ 2 cm. Sixteen patients (from Group C) had no residual disease; they attained a CR after conventional therapy and were enrolled in the study because they were considered to be at a very

TABLE 1
Patients' Characteristics at Time of Autologous Bone Marrow Transplantation

Patients characteristics	No. of patients/categories			Total no. of patients (evaluable)
	Group A[a]	Group B[b]	Group C[c]	
Age: median, 54 yrs (25–65)				
Peformance status				
0–1	4	4	21	29
2–3	4	3	1	8
FIGO stage				
IIIc	7	7	18	32 (13)
IV	1	—	4	5 (3)
Disease status at the time of ABMT				
Tumor masses > 2 cm	6	3	—	9 (7)
Tumor masses ≤ 2 cm	2	4	6	12 (9)
No residual disease	—	—	16	16 (0)
Total no. of patients (evaluable)	8 (8)	7 (2)	22 (6)	37 (16)

FIGO: International Federation of Gynecology and Obstetrics; ABMT: autologous bone marrow transplantation.
[a] Patients refractory to previous platinum-based chemotherapy.
[b] Patients treated in chemosensitive relapse.
[c] Patients treated in partial or complete response at the time of ABMT.

high risk of relapse: at the time of second-look surgery, 13 had residual malignant tumor masses ≤ 2 cm in greatest dimension totally removed by second-look debulking, and 3 had residual disease > 2 cm after initial debulking surgery and were in pathologic chemotherapy-induced CR. Sixteen patients were assessable for response, including the 8 patients of Group A, 2 of Group B, and 6 in PR of Group C. Twenty-one patients could not be evaluated for antitumor response: 5 of Group B, and the 16 of Group C in CR at the time of ABMT.

The median delay between diagnosis and time of ABMT was 30 months (range: 9–72 mos) for patients in Group A, 36 months (range: 19–60 mos) for patients in Group B, and 6 months (range: 6–8 mos) for patients in Group C. Patients in Group A and C were rapidly engrafted with a median delay of 1 to 5 months (range: 1–4 mos) after their last course of chemotherapy. Patients of Group B had had a median treatment free interval time of 18 months (range: 12–44 mos) before they were treated for their relapse.

Initial Evaluation

Before entering the study, each patient had a clinical evaluation that included physical examination, measurement of tumor marker levels, and an imaging work-up including computed tomographic (CT) scan, ultrasonography, chest roentgenography, and bone marrow biopsy. The condition of the patients was determined based on the usual biochemical profiles, complete blood counts, hepatic function tests, and creatinine clearance. The tumor marker levels (CA 125) were determined using an immunofluorescence method (Dyk Sangtec Laboratories, Dietzenbach, Germany). Informed consent was obtained from each patient.

Chemotherapy

Each of the 2 treatment arms consisted of a 5-day course of high doses of IFM, CBDCA, and VM-26 (ICT regimen) followed by ABMT. Each cycle consisted of the daily administration of VM-26 infused over 4 hours, followed by IFM infused over 6 hours; 7 hours after the end of IFM administration, CBDCA was infused over 6 hours. Sodium mercaptoethanesulfonate (mesna) was injected intravenously (i.v.) every 3 hours during a 12-hour period, starting at the same time as the IFM infusion. The mesna dosage was twice that of the IFM dose. Cryopreserved marrow was infused 120 hours after the end of the 5-day cycle, to avoid residual concentration of drugs in the blood, as previously described in our Phase I and II trial.[22] The second cycle was started when myeloid recovery had been obtained (polymorphonuclear leukocytes ≥ 1.5×10^9/L, platelets ≥ 50×10^9/L). Treatment was withdrawn in patients who did not respond to the first cycle, who relapsed too early after the first cycle, or who had suffered from extrahematologic, life-threatening Grade IV toxicity.

The expected major extrahematopoietic toxic effects were mucositis for VM-26, and renal damage for IFM and CBDCA. The maximum tolerated doses (MTDs) of the 3 drugs, defined by the unexpected occurrence of a single episode of World Health Organization (WHO) Grade III or Grade IV renal toxicity or

when a single death attributed to extrahematopoietic toxicity occurred, were previously determined in a large Phase I and II study, in which 44 patients, 24 of whom had ovarian carcinoma, received 74 cycles of therapy.[22,37] To select these MTDs, many dosages have been tested: for VM-26, from 150 to 200 mg/m^2/d × 5 days, for IFM, from 1500 to 2500 mg/m^2/d × 5 days, and for CBDCA, from 175 to 225 mg/m^2/d × 5 days. The dose-limiting side effects were renal toxicity and enterocolitis, supposedly due to the combination of IFM and CBDCA, and esophagitis, supposedly due to the use of VM-26 in very high doses. For these reasons, we considered that the MTDs of this tandem 3-drug therapy to be as follows: VM-26 150 mg/m^2/d for 5 days, IFM 1500 mg/m^2/d for 5 days, and CBDCA 200 mg/m^2/d for 5 days.

TABLE 2
Therapeutic Regimens Administered to the Patients

Combination therapy (mg/m^2/d × 5 days)			Total no. of courses delivered to the patients
VM-26	IFM	CBDCA	
175	2000	175	5
200	2250	200	1
200	1500	175	4
175	1500	175	1
175	1500	200	13
150	1500	200[a]	42

VM-26: teniposide; IFM: ifosfamide; CBDCA: carboplatin.
[a]These doses are considered to be the maximum tolerated doses (MTD) in this 3-drug combination. Twenty-nine patients received the 2 scheduled cycles of therapy; of these, 20 received the 2 cycles at the MTDs as described above. Eight patients received only the first course for various reasons.

Autologous Bone Marrow Transplantation and Supportive Care

ABMT and supportive care have been described previously.[22] Colony-stimulating factors [granulocyte-colony stimulating factor (G-CSF), granulocyte macrophage-CSF (GM-CSF)] were used when available for 6 patients.[37]

Evaluation of Toxicity, Response to Therapy, and Survival

Toxicity was evaluated according to the WHO classification.[36] However, esophageal toxicity was graded as follows: Grade 0, absent; Grade I, mild pain, normal alimentation possible; Grade II, painful dysphagia, only liquid alimentation possible; Grade III, pain requiring major analgesics, alimentation impossible: Grade IV, esophageal perforation. Clinical CR to therapy was defined as the complete disappearance of all evidence of tumor by physical examination, radiographs (including CT) and the normalization of CA-125. Post-treatment laparotomy was not required to document a CR, but could be envisaged if possible. Pathologic CR could be thus defined as the complete disappearance of tumor including negative systematic biopsies and negative peritoneal washing. Partial response, stable disease, and progressive disease were defined by radiographs (including CT) according to the WHO classification. The patients who died of therapy were considered treatment failures. The durations of the overall survival were calculated according to the Kaplan–Meier method, from the date of the first intensive course.[38] Patients who obtained a CR did not receive further therapy.

RESULTS

Toxicity

The 37 patients included in the study were evaluated for toxic side effects. Twenty-nine patients received the 2 scheduled cycles of therapy. The median interval between the start of the first cycle and the start of the second was 35 days (range: 28–56 days). Eight patients received only the first cycle for various reasons: 2 (1 from Group B, 1 from Group C) died during their first course, 2 had reversible Grade IV esophageal toxicity, 1 with reversible Grade IV renal toxicity and 1 with Grade IV diarrhea with severe acute pancreatitis, and 3 failed to respond to the first course (1 from Group A) or relapsed early after the first (2 from Group C). A total of 66 cycles of therapy were given to the 37 patients. Sixty-five cycles could be evaluated for toxicity: 24 with various levels of the 3 drugs and 41 with the 3-drug MTDs, as described above (Table 2).

Extrahematopoietic Toxicities

Oropharyngeal and esophageal side effects

Oropharyngeal mucositis occurred in 58 of 65 cycles (89%) and was severe (WHO Grade III–IV) in 34 of 65 cycles (52%); esophagitis was observed in 59 of 65 cycles of therapy (90%) and was severe (WHO Grade III–IV) in 15 of 65 cycles (23%). The 2 life-threatening episodes of Grade IV esophagitis occurred during the first course at a daily VM-26 dose of 175 mg/m^2/d × 5 days. One patient was cured by prolonged antifungeal therapy, antibiotherapy, and parenteral alimentation; the second one, who had had an upper-third esophageal perforation, needed surgical therapy.

Gastrointestinal and hepatic toxicities

Of the 65 therapeutic cycles, 63 (97%) were complicated by diarrhea. Grade III diarrhea occurred in 24 cycles (37%) and Grade IV diarrhea was recorded in 9 cycles (14%). One patient developed reversible severe acute pancreatitis with acute Grade IV diarrhea. The percentage of Grade IV diarrhea, when the drugs were administered at their MTDs, was quite low: 6 out of

TABLE 3
Extra-Hematopoietic Toxicities of the Treatment (WHO Grade)

	Total no. of cycles with toxic effects (first course/second course)				
Toxic effect	0	I	II	III	IV
Mucositis	7 (4/3)	5 (3/2)	19 (9/10)	26 (15/11)	8 (6/2)
Esophagitis	6 (2/4)	8 (5/3)	36 (20/16)	13 (8/5)	2 (2/0)
Renal	24 (15/9)	27 (11/16)	12 (9/3)	1 (1/0)	1 (1/0)
Diarrhea	2 (0/2)	6 (4/2)	24 (13/11)	24 (13/11)	9 (7/2)
Peripheral neuropathy	46 (26/20)	9 (4/5)	8 (5/3)	2 (2/0)	0
Hepatic dysfunction					
Transaminases	45 (26/19)	12 (5/7)	8 (6/2)	0	0
Alkaline phosphatase	57 (32/25)	5 (2/3)	3 (3/0)	0	0
Bilirubin	55 (30/25)	6 (4/2)	4 (3/1)	0	0

WHO: World Health Organization.

41 evaluable cycles administered (14%). At least 1 sign of biologic hepatic toxicity was observed in 12 cycles of chemotherapy (18%). No Grade III or IV hepatic toxicity was observed. No venoocclusive disease was observed.

Renal toxicity

Two patients had severe nephropathy during their first course; of these, 1 had reversible Grade III nephrotoxicity with Grade IV diarrhea and acute pancreatitis, and the other had reversible Grade IV nephropathy with Grade IV esophageal toxicity. These two patients did not receive the second course of therapy.

Neurologic toxicity

Central nervous system toxicity (hallucinations, lethargy) of moderate intensity occurred in 3 patients (8%) and was always reversible. Fourteen patients (38%) had Grade I or II peripheral neuropathy and 2 had reversible Grade III peripheral neuropathy. Transitory impaired hearing occurred in 4 patients.

Cutaneous toxicity

Four patients (11%) had transient VM-26-related erythematous, maculopapular rashes. No therapy was prescribed and, in particular, no corticosteroids were administered to these patients.

Hematologic Toxicity

Sixty-three cycles of therapy were available for evaluation: the 3 patients who died of therapy (2 at the first course and 1 during the second) were in aplasia at their time of death. The median durations of granulocytopenia ($< 0.5 \times 10^9$/L) was 20 days for the first cycle (range: 12–32) and 19 for the second (range: 8–30). Those of thrombocytopenia ($< 50 \times 10^9$/L) were 16 days (range: 8–22) and 18 days (range: 12–22) for the first and the second cycle, respectively. Only 6 patients received G-CSF or GM-CSF, both at 10 ng/kg/d, therapy for a total number of 7 cycles. Fever $\geq$ 39 °C was recorded during all the cycles of therapy. Aplasia was complicated by documented septicemia in 10 cycles (15%) (*staphylococcus epidermidis,* 5; *staphylococcus aureus,* 1; *klebsiella pneumoniae,* 1; *pseudomonas paucimobilis,* 1; *candida glabrata,* 1; and *candida albicans,* 1).

Therapy-Related Deaths

Three patients (8%) died of therapy-related complications: 2 during their first course and one during the second. One patient (Group B) died of systemic candida infection, one (Group C) died suddenly of unknown cause: at the time of death, she had Grade II renal toxicity, and nonhaemorrhagic Grade IV diarrhea. Autopsy did not reveal the cause of death and did not shown any residual tumor masses. The third patient (Group C) died on Day 10 during her second course of unexpected and acute IFM-related pulmonary edema. The 2 patients (9%) of the 22 from Group C who died of therapy-related complications had been given the 3 drugs at their MTDs.

Response to Therapy

Sixteen patients out of the 37 in the study were evaluable for response to high dose therapy: 8 from Group A, 2 from Group B, and 6 from Group C. Among the 8 patients from Group A, 1 attained a CR of 10 months, and 4 attained a PR (5–10 mos). The 2 evaluable patients from Group B achieved PRs of 7 and 12 months. Unfortunately, no CR was observed in this group of patients. Among the 6 evaluable patients in Group C, 1 achieved a surgically confirmed CR of 57 months and then relapsed, and 1 attained a PR of 10 months. The 2 CRs observed in this study were obtained for

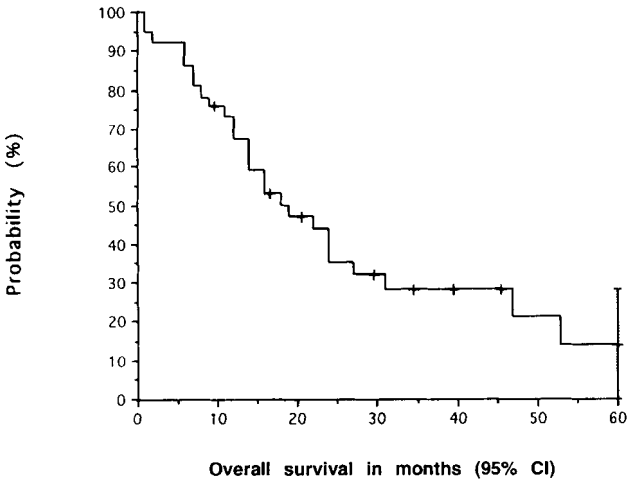

FIGURE 1. Overall survival in months (95% confidence index) of the whole population is shown. The duration of survival is determined since the time of bone marrow transplantation.

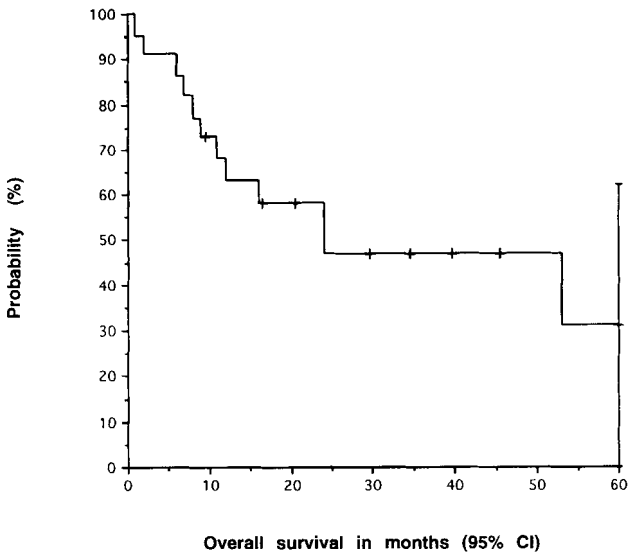

FIGURE 2. Overall survival in months (95% confidence index) of the 22 patients from Group C is shown. The duration of survival is determined since the time of autologous bone marrow transplantation.

patients with tumor masses $\leq$ 2 cm at the time of ABMT.

For the whole population, the overall response rate to high dose therapy and ABMT was 56% (95% confidence interval [CI], 40–72%) including 2 CR (12%) and 7 PR (44%). No CR of long duration and no long term survival were observed among the 5 patients treated with Stage IV ovarian cancer.

Survival

The median overall survival duration of the whole population of patients was 18 months (range: 1–63+ mos) since the time of ABMT. The survival rate of this population was 14% at 60 months. The median overall survival duration for the 22 patients in Group C was 24 months (range: 1–63+ mos) since the time of ABMT. The survival rate at 60 months was 32%. Of these 22 patients, 2 died of toxic side effects, 10 died of their disease, and 10 are alive: 4 in relapse from 10 to 57 months, and 6 in continuous CR from 9 or more to 63 or more months. Among this group of 6 patients, 3 were grafted in pathologic chemotherapy-induced CR and 3 in CR obtained by second-look surgery.

DISCUSSION

Levin and Hryniuk have reviewed and reported the importance of dose intensity in the treatment of advanced ovarian cancer. Considering 33 different first line chemotherapy trials, using CP-based treatment, they have shown that the prognosis and outcome including clinical response and survival rates were correlated with the dose intensity of therapy effectively delivered to the patients. The relationship is strongest with CP, one of the most active single drugs in ovarian tumor. The association between outcome and dose intensity of platinum alone or in combination was statistically significant. If for CPM the results are not convincing, there is some evidence that the use of CPM increases the efficacy of single-agent platinum.[39,40] Several studies have shown the antitumor efficacy of high-dose CP in patients with ovarian cancer refractory to low-dose CP. With a high dose CP regimen, a response rate of 20 to 32% can be achieved in patients refractory to standard low dose CP, but the combination of high doses of CBDCA, a more suitable drug for its use in high doses than CP, with an epipodophyllotoxin derivative and IFM, is preferable.[41,42] In this study we report the results of a Phase I or II trial of tandem high dose chemotherapy with IFM, CBDCA, and VM-26 with ABMT for the treatment of poor-prognosis common epithelial ovarian carcinoma.

Concerning the toxicities, oropharyngeal mucositis was not a dose limiting factor, contrary to the esophageal toxicity. Grade IV esophagitis was observed at doses of VM-26 $\geq$ 175 mg/m^2/d $\times$ 5 days. This led us to set up the MTD, as previously described, at 150 mg/m^2/d $\times$ 5 days.[22] Until now, severe esophagitis had not been recognized as a toxic effect of high dose VM-26. Grade IV diarrhea was observed in only 9 of 65 cycles (14%) of therapy and, as previously discussed, may be the result of synergistic toxicity between CBDCA and IFM. Renal toxicity was acceptable. We observed one Grade III and one Grade IV renal toxicity, rapidly reversible for the 2 patients without the necessity of hemodialysis. Nephrotoxicity is related to the use of high dose IFM, especially in patients

previously treated for a long period of time with CDDP.[43,44] The role of high dose chemotherapy in the appearance of these toxic side effects has already been discussed.[23] We had to regret one unexpected lethal episode of IFM-related acute pulmonary edema. This toxic side effect has already been reported.[45] Finally, hepatic tolerance, central nervous system, and cutaneous toxicity occured as expected, and were acceptable.

The MTDs of the 3 drugs have been, according to the toxicities which were observed in the first part of our trial, set up at 750, 7500, and 1000 mg/m^2 for VM-26, IFM, and CBDCA, respectively.[22] The MTD of VM-26 used as single agent therapy has been set up at 1000 mg/m^2.[25] The MTDs of IFM and CBDCA have been redefined in the second part of our work for patients with refractory germ-cell tumors and metastatic trophoblastic disease, according to the data published worldwide. These MTDs have now been set up at 12,000 and 1500 mg/m^2, respectively, with VP-16 used at a total dose of 1500 mg/m^2.[23] For patients with advanced ovarian cancer, it could be difficult in a situation of consolidation therapy to increase the doses of the 3 drugs given in tandem therapy. The toxic death rate for patients in Group C was high for 2 out of 22 patients (9%). Minimizing the risk of toxic death is an important challenge. For this reason, we have, for the first time, considered in this therapeutic approach of tandem therapy for patients treated in PR or in CR that the MTDs of VM-26, IFM, and CBDCA must be set up as described above. These doses are less than the MTDs of these 3 drugs used as single agents (1000, about 20,000, and 2,400 mg/m^2, respectively), but our tandem high dose therapy enables us to give in a median delay of 5 weeks a total dose of VM-26 fixed at 1500 mg/m^2, of IFM fixed at 15,000 mg/m^2, and of CBDCA fixed at 2000 mg/m^2. Concerning the choice of the three drugs of this preperative regimen, the place of IFM for the treatment of GCTs has to really be discussed because its use could prevent the administration of the epipodophyllotoxin and mainly of CBDCA at higher doses. For CBDCA, the MTD could be set up at 1500 to 2000 mg/m^2, in association with VP-16 at 1500 to 1800 mg/m^2.[21,23] For VM-26, no data are available concerning its use at high doses in association with IFM and CBDCA. The use of VP-16 instead of VM-26 has yet to be discussed in the field of ovarian tumors: (1) the response rate of advanced ovarian carcinoma to VM-26 is a much debated question; and (2) some published trials reporting the efficacy of VP-16 given i.v., by mouth, or by intraperitoneal route with CDDP or CBDCA are now available.[6,24,46–49] According to these data and to our previous experience, our conclusions in terms of choice of intensive regimen and of MTDs of the drugs used in our trial have to be reconsidered for further studies. The introduction of hematopoietic growth factors and the use of peripheral blood stem cells rescue could certainly enable us to increase the MTDs of the epipodophyllotoxin agents and of CBDCA and IFM.

In regard to the response rate and the results in terms of survival, we observed a response rate to ABMT of 56% with a CR rate of 12%. One CR was observed in a patient from Group A refractory to CP therapy but was, unfortunately, of very short duration. No CRs were observed for the patients from Group B who were treated in a situation of chemosensitive relapse. No long term survival was reported. So we cannot recommand such high dose therapy for patients primarly resistant to CDDP or in relapse, even in a situation of chemosensitive relapse. For patients in Group C treated with consolidation therapy, one CR lasting 57 months was observed. For this group of patients, the survival rate since the time of ABMT was 32% at 60 months with a median survival time of 24 months. These results in a highly selected population were similar to the results reported in the literature with conventional CP-based therapy. This Phase I or II trial of tandem therapy is however feasible with good tolerance and acceptability, and can deserve interestingly further indispensable randomized studies employing VP-16 with CBDCA or the same drugs with IFM.

The results of high dose therapy with ABMT for the treatment of advanced epithelial ovarian carcinoma are unfortunately often uninterpretable (Table 4). This is due to the small number of patients enrolled in various trials, brief follow-up durations, major differences in cytoreductive regimens (including alkylating agents alone or in combination therapy, sometimes combined with whole abdominal irradiation, or intraperitoneal therapy with CP), major differences in tumor burdens, various disease status at the time of ABMT, difficulty to surgically confirm a situation of clinical PR or CR, and the most important point, frequent inclusion of patients with refractory disease, rather than drug-sensitive ovarian tumors.

High dose regimens used for high dose therapy are different from one study to another.[50–57] High objective response rates have been observed both in sensitive and refractory heavily pretreated patients. However, the durations of response for the latter population of patients are short, and the impact on survival for chemosensitive patients remains undetermined because no randomized trials have been performed. Dose intensity or dose per unit time may be a more important determinant of outcome because Levin and Hryniuk have demonstrated a direct relationship between dose intensity of platinum therapy and survival. Multiple applications, rather than a single course

TABLE 4
Summary of High-Dose Chemotherapy Trials in Advanced Ovarian Cancer

Reference no.	Total no. of evaluable patients (FIGO stage)	Disease status[a] no. of pts	Refractory (yes/no)	ABMT regimen[b] (MTD mg/m^2)	Response CR (%) (duration in mos)	PR (%)	Survival (time)
50	11/11 (Ic: 1; III: 6; IV: 4)	micro: 8 macro: 3	yes	CPM 7,000 VP-16: 1,000	6 (55) (median: 15+)	—	2 CCR (43+, 75+ mos)
51	14/– (II: 1; III: 12; IV: 1)	micro: 5 macro: 9	yes: 2 no: 12	L-PAM: 140	no data (30–60+)		DFS: 33% at 3 years
52	35/12 (III: 30; IV: 5)	micro: 9 macro: 26 <2 cm: 10 >2 cm: 16	yes: 8 no: 27	L-PAM: 240	4 (33)	5 (42)	47% (54 mos)
53	12/8 (III: 6; IV: 6)	macro: 12	yes	CPM: 5625 TTP: 300 DDP[c]: 150	— (3–9)	6 (75)	—
54	13/12 (III/IV)	clinical CR	no	DDP: 100 VP-16: 600 CB: 1800	6 (55)[d]	3 (27)	no data
55	9/8 (III: 8; IV: 1)	WRD: 6 NRD: 2	yes: 6 no: 3	IFM: 10,000 CB: 1500	5 (63) (3–23)	2 (25)	PFS: 6 mos
56[e]	42 (Ic-IV)	NRD: 22 (Group A) WRD: 20 (Group B)	?[*e] ?[*e]	CPM: 4800 ADM: 200 DDP: 300 (tandem)	— no data	—	A: 78% (5 yrs) B: 26% (5 yrs)
57	7/6 (no data)	macro: 7	yes	MTN: 75 CPM: 120[f] CB: 1500	5 (83) (3–30+)	1 (17)	3–34+ mos
[g]	37/16 (IIIc: 32; IV: 5)	>2 cm: 9 ≤2 cm: 12 NRD[d]: 21	yes: 8 no: 29	VM26: 750 IFM: 7500 CB: 1000 (tandem)	2 (12)	7 (44)	14% (5 yrs)

[a] Micro/Macro: microscopic/macroscopic disease at the time of ABMT.
[b] L-PAM: melphalan; TTP: thiotepa; ADM: adriamycin; MTN: mitoxantrone; CB: carboplatine (CBDCA).
[c] Intraperitoneal administration.
[d] Pathologic CRs.
[e] mg/kg.
[f] High dose therapy delivered as first-line therapy.
[g] This study.
FIGO: International Federation of Gynecology and Obstetrics; ABMT: autologous bone marrow transplantation; MTD: maximum tolerated dose; CR: complete response; PR: partial response; CCR: continuous CR; DFS: disease free survival; PFS: progression free survival; NRD: no residual disease; WRD: with residual disease.

could represent a superior strategy: for this reason we chose in the past to give a second round of high dose therapy. However, if tandem therapy seems to be of value for the treatment of GCTs, we have no sufficient data to propose 2 consecutive high dose intensifications rather than a single one for the forthcoming randomized studies.

Concerning disease status of the patients at the time of ABMT, it is established that high dose therapy, unfortunately, is unable to overcome resistance of ovarian tumors to conventional chemotherapy durably. Platinum sensibility, as well as low tumor burden, is probably the most important prognostic factor in patients undergoing high dose therapy.[58] Interestingly, high dose therapy with ABMT was sometimes immediately and successfully delivered after initial debulking surgery and was in these cases, the sole chemotherapeutic approach of the disease.[56] We agree with most authors that the most appropriate population of patients in whom high dose therapy can be explored and evaluated is represented by groups of patients with minimal residual disease after second-look surgery, and by patients in surgically-documented CR but with criteria of long term poor prognosis.[59] The concept of high dose therapy must be applied in a real spirit of high dose therapy. New therapeutic schemes with taxol delivered in higher doses (> 250 mg/m^2) in combination with high dose CPM, and rapidly sequenced

high dose chemotherapy delivered in a short period of time with peripheral blood stem cells support is a very interesting investigational outlook.[60] Experiences of the past decade, and the use of peripheral blood stem cells rescue with hematopoietic growth factors rather than bone marrow rescue often contaminated by occult micrometastases, could enable us to realize this approach of high dose therapy.[61] In conclusion, after completing the Phase I or II trials, and considering the financial cost of these therapeutic approaches, prospective, randomized studies with adequate control arms are required to evaluate the activity of high dose therapy in poor-prognosis ovarian carcinoma. The ongoing studies will need long term follow-up before any definitive conclusions can be made regarding efficacy in terms of response and survival.

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