

## **Pilot Study of a High-Dose Carboplatin-Based Salvage Strategy for Relapsing or Refractory Germ Cell Cancer**

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### **ABSTRACT**

*Eleven patients with germ cell cancer relapsing from a complete remission and 7 patients with refractory germ cell cancer and/or an unresectable partial remission received salvage chemotherapy with one to two courses of carboplatin ( $800 \text{ mg/m}^2$ ) and etoposide ( $500 \text{ mg/m}^2$  on days 1, 3, and 5), followed by either one or two courses of carboplatin ( $1600 \text{ mg/m}^2$ ), cyclophosphamide ( $6 \text{ g/m}^2$ ), and thiotepa ( $480 \text{ mg/m}^2$ ) divided over 4 days with autologous bone marrow transplantation and/or peripheral stem cell support. Eight of 11 relapsing patients (73%) were salvaged (with a follow-up of 21+ to 56+ months), but only 1 of the 7 refractory patients survived (34+ months). The high-dose carboplatin-based salvage regimen is feasible and deserves further evaluation in patients relapsing from a complete remission. Even more intensive treatment strategies may be required to salvage patients who are refractory to standard doses of platinating agents.*

### **INTRODUCTION**

Patients with germ cell cancer who fail to achieve a complete remission with standard cisplatin- or carbo-

platin-based chemotherapy or who relapse from a chemotherapy-induced first remission face a poor prognosis, with a long-term disease-free survival rate of only 25% (1,2). Second-line combination chemotherapy with

cisplatin, ifosfamide, and vinblastine after first-line therapy with cisplatin, etoposide, and bleomycin has been shown to achieve cure in only 23% of patients (3).

After early disappointing experiences with high-dose chemotherapy in germ cell cancer (4), this treatment modality has regained interest after it was shown that it can produce long-term remissions in about 15% of patients thought to be "incurable" with conventional approaches (5). Incurable patients include those who have "refractory" disease [defined as patients with progression or an unequivocal rise of serum- $\beta$  human chorion gonadotrophin ( $\beta$ HCG) and/or alpha-fetoprotein (AFP) within 4 weeks of the last cisplatin or carboplatin dose] and patients who relapse after or do not respond to second-line chemotherapy. This finding has led to studies in which intensive chemotherapy with bone marrow support has been administered in an earlier stage of the disease (6). One randomized study has failed to show benefit for consolidation treatment in first-line therapy, but several small, nonrandomized studies in second- and third-line situations have yielded encouraging results (see for review Ref. 7).

Since it is difficult to define a category of patients with a very high risk of not being cured by first-line therapy in germ cell cancer, the earliest and potentially most favorable time for high-dose chemotherapy may be relapse after first-line chemotherapy or immediately after the first proof of refractory disease has been obtained. It is also reasonable to assume that phenomena such as recruitment of quiescent cells and kinetic drug resistance could occur after chemotherapy in germ cell cancer, as in other tumors, and that repeated therapy courses could thus be superior to a single one. We have previously found that a salvage regimen with a double-standard carboplatin dose and a substantially increased etoposide dose could induce remissions in the large majority of patients in second-line therapy (8), but that these remissions were not durable and thus required some type of consolidation. We now report the results of a feasibility study, in which treatment with high-dose carboplatin/etoposide was followed by one or two courses of very-high-dose chemotherapy with carboplatin, cyclophosphamide, and thiotepa (CTC) with autologous bone marrow or stem cell support. The high-dose regimen was selected because of the theoretical attractiveness of a triple-alkylator combination in potentially etoposide-resistant disease (9). Although the efficacy of standard-dose thiotepa in germ cell cancer has not been studied, it appears reasonable to assume that it has some activity, since it is a classical alkylator. In addition, thiotepa virtually lacks extramedullary toxicity up to a dose of 20

$\times$  standard, allowing substantial dose escalations in the autologous transplantation setting (10), and it readily crosses the blood-brain barrier. The latter property is obviously highly desirable in a disease that frequently spreads to the central nervous system at relapse.

## PATIENTS AND METHODS

### Patient Selection

All patients had biopsy-proven germ cell cancer and either had relapsed after adequate first-line treatment or had failed to achieve a complete remission or resectable partial remission. Adequate first-line treatment was defined as 4–6 courses of cisplatin- or carboplatin-based chemotherapy, followed by surgery in case of residual disease with normal tumor markers. Proof of progression was obtained by rising tumor markers (AFP or  $\beta$ HCG), or by documentation of new or growing lesions, when clinically indicated, followed by biopsy to exclude mature teratoma. Patients who had failed more than one prior regimen were also eligible. Adequate bone marrow function [white blood cell count (WBC)  $\geq 3.5 \times 10^9$  and platelets  $\geq 100 \times 10^9$ ] and renal function (creatinine clearance  $\geq 50$  ml/min) were required. No patient was excluded on the basis of age or performance status. Preexisting cisplatin-associated neuropathy or hearing loss was accepted.

All patients were fully informed of the investigational nature of the treatment and informed consent was obtained according to institutional guidelines. The study was approved by the institutional ethical committee.

### Pretreatment Evaluation

Baseline investigations included physical examination, complete blood count with differential, serum chemistries, chest roentgenograms, and computerized tomography (CT) scan of the chest and of the abdomen.  $\beta$ HCG and AFP were also determined. Additional investigations, such as CT scans of the brain, were done as indicated by history or clinical findings.

### Bone Marrow and Stem Cell Harvests

Bone marrow was harvested by multiple aspirations from the iliac crest under general anesthesia. A total of at least  $2 \times 10^8$  nucleated cells per kg body weight had to be obtained. The theoretical number of granulocyte-macrophage colony-forming units (CFU-GM) available

for reinfusion (as indicated by colony-forming assays after freezing and thawing of aliquots) had to exceed  $2 \times 10^4$  per kg body weight.

Autologous peripheral stem cells were mobilized by administering chemotherapy followed by daily s.c. administration of 300  $\mu\text{g}$  granulocyte colony-stimulating factor (G-CSF, Neupogen<sup>®</sup>, received as a gift from Amgen, Breda, The Netherlands). The mobilizing chemotherapy regimen consisted of ifosfamide (4 g/m<sup>2</sup>) and mesna (3200 mg/m<sup>2</sup>), both on day 1, and etoposide (100 mg/m<sup>2</sup>) on days 1, 2, and 3. G-CSF was started on day 4. From day 11 on, daily blood counts and estimates of the CD34-positive nucleated cell fractions in the peripheral blood were performed by fluorescence-activated cell sorting employing an anti-CD34 antibody (11) (HPCA-2 FITC, Becton Dickinson, Mountain View, CA). Daily hemapheresis sessions began as soon as an unequivocal rise in CD34-positive cell percentage was observed. A total yield of  $10 \times 10^6$  CD34-positive cells per kg body weight was considered adequate for a double transplantation procedure (12), but a lower number was accepted when 2 separate mobilization procedures led to a smaller harvest. High-dose chemotherapy was begun immediately upon bone marrow recovery after the stem cell mobilization procedure.

### Treatment Protocol

The salvage strategy consisted of the subsequent administration of three courses of high-dose carboplatin-based chemotherapy, complemented by surgery in case of resectable disease. Two different high-dose carboplatin-based regimens were employed:

**HD-CE** (8) consisted of carboplatin (800 mg/m<sup>2</sup>) on day 1 and etoposide (1500 mg/m<sup>2</sup>) divided over days 1, 3, and 5. From the time at which it became commercially available, G-CSF was administered s.c. from day 6 onward in a dose of 300  $\mu\text{g}$  s.c. (regardless of body weight) and was continued until the WBC count exceeded  $5.0 \times 10^9/\text{L}$ .

**CTC** (13) incorporated carboplatin (1600 mg/m<sup>2</sup>), thiotepa (480 mg/m<sup>2</sup>), and cyclophosphamide (6000 mg/m<sup>2</sup>), divided over 4 days. In patients with impaired renal function (defined as a creatinine clearance below  $110 \text{ ml} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$ ), the carboplatin dose was adjusted according to a modified "Calvert formula" (14):

Total dose of carboplatin (mg) =  $20 \times [\text{creatinine clearance (ml/min)} + 25]$

This formula leads to an "area under the curve" of carboplatin that is roughly four times that used in standard-dose carboplatin combinations. Mesna (500 mg) was given 6 times daily for a total of 24 doses, beginning 1 hr before the first cyclophosphamide infusion. From patient 12 on, mesna was continued for another 2 full days (after severe hemorrhagic cystitis had been observed in the 2nd course of patient 11, see below). Bone marrow and/or peripheral stem cells were reinfused 48–72 hr after the discontinuation of chemotherapy.

The first 10 patients (part A of the study) received two courses of HD-CE (the second starting on day 28 of the first), followed by a single course of CTC (beginning on day 28 of the second HD-CE course) with autologous bone marrow support. After the advent of peripheral stem cell support allowed double transplantations, the next 8 patients (part B of the study) received a single course of HD-CE followed by two courses of CTC, the first of which was begun on day 28 of the HD-CE course, and the second on day 35 of the first CTC course (day 28 after the first stem cell reinfusion). Before the second course of CTC was started, the patients were required to have had adequate granulocyte counts ( $>2.0 \times 10^6/\text{L}$ ) for at least 1 week, and any infections of nonhematological toxicities had to be resolved. Platelet transfusion independence was not required. All patients undergoing a double transplantation procedure received autologous peripheral stem cell support without additional bone marrow transplantations. One-half of the harvested material was reinfused after each course of CTC.

### Supportive Care

The supportive care during and after HD-CE courses has been reported previously (8). Antibiotic prophylaxis was employed with ciprofloxacin 1000 mg (divided over 2 daily oral gifts) and amphotericin suspension 2000 mg (divided over 4 daily oral gifts). Cultures of throat, stool, and both Hickman catheter lumens were performed each week to check for growth of microorganisms resistant to these antibiotics. Platelet transfusions were given as required to maintain platelet counts above  $10 \times 10^9/\text{L}$ .

Antibiotic prophylaxis after CTC and bone marrow or stem cell transplantation consisted of ciprofloxacin and amphotericin suspension as after HD-CE, but also incorporated i.v. infusion of  $1 \times 10^6$  units penicillin daily  $\times$  4 and 0.25 mg/kg amphotericin B daily, from the day of bone marrow or stem cell reinfusion until the granulocyte count exceeded  $0.5 \times 10^9/\text{L}$ . From the time it became commercially available, G-CSF was administered s.c.

from the day of bone marrow reinfusion in a dose of 300  $\mu\text{g}$  s.c. (regardless of body weight) and was continued until the WBC count exceeded  $5.0 \times 10^9/\text{L}$ . All patients who underwent peripheral stem cell transplants received G-CSF.

## RESULTS

Between August 1989 and September 1992, all 18 patients who presented at the Netherlands Cancer Institute with relapsing or refractory nonseminoma germ cell tumor were entered on the trial. Pertinent patient characteristics are given in Table 1. In the first part of the study (part A), 10 patients were scheduled to receive two courses of HD-CE followed by a single CTC course. The second part (part B) could be initiated when the technology of autologous peripheral stem cell transplantation became available, and 8 patients were to receive a single HD-CE course, followed by two courses of CTC.

Table 1

Patient Characteristics

Number of patients	18
Male	18
Female	0
Median age (years)	31 (range: 19–53)
Median WHO performance status	1 (range: 0–2)
Tumor type	
Teratoma	6
Choriocarcinoma	2
Seminoma + other components	6
Mixed tumors without seminoma	2
Pure embryonal	1
Uncertain <sup>a</sup>	1
Elevated tumor markers	
LDH	5
$\beta\text{HCG}$	8
AFP	8
Site of residual disease	
Retroperitoneal nodes	9
Lung	8
Mediastinum	7
Brain	2
Bone	2
Liver	1
Cervical nodes	1
Adrenal gland	1
Tumor markers only	2

<sup>a</sup>Patient with large mediastinal tumor. In bronchial biopsy, large-cell undifferentiated carcinoma.  $\beta\text{HCG} > 100,000$  U/ml.

## Feasibility of the Planned Treatment

Four of the 18 patients (all from the "poor-risk group," see below) were not able to undergo a CTC course with the associated autotransplantation procedure. The reasons for this were as follows: Patient 3 died of a systemic *Aspergillus* infection in the neutropenic period following his first HD-CE course. Patient 7 developed neutropenic fevers and unexplained infiltrates on his chest roentgenogram in both neutropenic periods of the two HD-CE courses. G-CSF and peripheral stem cell technology were not yet available at that time and the patient was not considered fit for transplantation. Two patients (numbers 6 and 18) did not respond to the HD-CE courses and were taken off study. One of these also had poor platelet recovery after transfusion, as a result of HLA sensitization, precluding exposure to the prolonged platelet transfusion dependence associated with transplantation procedures.

Thus, 14 of 18 patients went on to transplantation and received a total of 19 CTC courses. Two patients, both scheduled to receive a second transplant, went off study because of an unfavorable response to the first CTC course. Patient 13 had progression of a previously responsive CNS localization, and patient 17 failed to achieve normalization of his  $\beta\text{HCG}$  (which was considered to predict incurability even with a second CTC course).

There were no toxic deaths as a result of the 19 transplantation procedures, and all patients in part B of the study who had received the first transplantation procedure were considered to be physically able to tolerate a second one at the planned time. The second CTC courses were actually started on days 28, 28, 28, 29, and 32 after the previous stem cell reinfusion.

## Toxicity

The toxicities of the two chemotherapy regimens have been described in detail previously (8,13). These reports included some toxicity data and some preliminary survival data of 9 patients described in this study. (Toxicity data of the HD-CE regimen in patients 1–6 were published in Ref. 8 and the toxicity of the CTC regimen in patients 1, 2, 4, 5, 8, 9, and 10 was described in Ref. 13.)

Briefly, the main toxicity of the HD-CE regimen consisted of profound bone marrow suppression with platelet transfusion dependence in all courses and absolute neutropenia. Nausea and vomiting were mild with dexamethasone and ondansetron as antiemetics. Grade

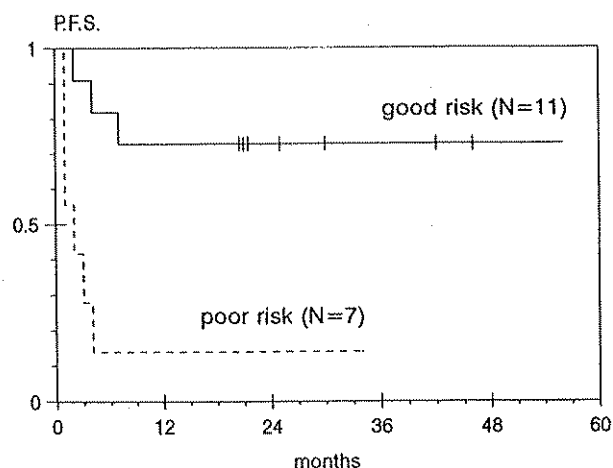
I–III mucositis occurred in most patients. Bone marrow recovery after the first HD-CE course was complete on day 28 in all patients, and no dose modifications or delays of the subsequent courses were required (part A of the study).

The main toxicities of the CTC regimen consisted of bone marrow suppression, nausea and vomiting, and slight elevation of liver enzymes in all patients. Minor to moderate mucositis, varying degrees of diarrhea, and skin rashes were observed in most. Patient 9 experienced moderate to severe organ toxicity, including reversible cyclophosphamide-associated pancarditis, renal toxicity (maximum serum creatinine 293  $\mu\text{mol/L}$ ), and reversible hearing loss and tinnitus (13). All signs of toxicity including symptomatic ototoxicity abated in the weeks following transplantation.

### Toxicity and Engraftment in Patients Undergoing Double Transplantations

Five patients (numbers 11, 12, 14, 15, and 16) underwent two closely spaced treatments with CTC followed by peripheral stem cell reinfusions. The second course of CTC was well tolerated in all patients, except patient 11, who developed severe hemorrhagic cystitis after the second course. The patient, who had a refractory extragonadal teratoma (mediastinal and retroperitoneal), died 72 days after the second transplantation of disease progression and a chronic myeloid leukemia–like myeloproliferative syndrome. The hemorrhagic cystitis had not subsided at that time. Increase in severity of a preexisting cisplatin-associated neuropathy was possibly seen in patient 11, but in none of the other 4 patients who received a second CTC course. Reversible tinnitus occurred in all and (reversible) symptomatic hearing loss in 2 patients.

The median number of mononuclear cells reinfused in each procedure was  $2.8 \times 10^8/\text{kg}$  (range: 2.4–5.6), the median number of CFU-GM was  $85.5 \times 10^4/\text{kg}$  (range 30–120.5), and the median number of  $\text{CD34}^+$  cells was  $3.8 \times 10^6/\text{kg}$  (range 2.7–8.2). The engraftment parameters varied not significantly between the first and the second course in individual patients. A granulocyte count of  $0.5 \times 10^9/\text{L}$  was reached on day 11 (range 10–12) after reinfusion in both courses. Platelet transfusion independence (defined as a stable or increasing platelet count of at least  $20 \times 10^9/\text{L}$  not requiring platelet transfusions) was achieved on day 18 (range 12–28) after reinfusion. The platelet transfusion requirement after the second CTC second course (median number of transfusions 8, range 5–19) was somewhat higher than after the



**Figure 1.** Progression-free survival after start of salvage treatment of all patients entered in the study (including those who did not undergo autotransplantation). *Good-risk* patients were those who had relapsed from a first or second complete remission, irrespective of the number of chemotherapy regimens received. *Poor-risk* patients were those who had refractory disease, or who had progression without ever having achieved a complete remission with standard-dosed chemotherapy.

first one (median 5, range 4–11). This was due in part to the occurrence of hemorrhagic cystitis in 1 patient after the second CTC course.

### Efficacy

Of the 18 patients entered in the study, 9 were in unmaintained complete remission (CR) at the time of this writing. The 8 evaluable patients who were not cured by the salvage regimen, all progressed within 7 months of the start of treatment. The median time to progression was 2.5 months. Of the 5 patients who progressed after undergoing at least one transplantation procedure, all relapsed within 4 months of the (last) transplantation.

Retrospectively, the patients can be divided in two risk groups (Fig. 1). Patients who relapse from a first or second complete remission can be considered to have a “good risk.” Patients who have either an unresectable partial remission (UPR) after adequate first-line treatment or who have tumors refractory to standard-dose chemotherapy may be considered to be “poor-risk” patients. Refractory tumors are defined as tumors showing progression or rise in tumor markers within 4 weeks of the last administration of cisplatin or carboplatin.

The pretreatment characteristics and outcomes for the good-risk patients are shown in Table 2. Eight of 11

**Table 2**  
*Pretreatment Characteristics of the "Good-Risk" Patients*

Patient number	Part of the study	Number of relapse	Extragonadal primary	Prior chemotherapy	Number of regimens	Months since last chemotherapy	Outcome	RFS (months)
1	A	1st	No	BOP/VIP	1	4	NED	56+
2	A	1st	No	BEP	1	4	NED	46+
4	A	1st	Mediastinal	BEP	1	14	NED	42+
5	A	1st	Mediastinal	BOP/VIP	1	6	DOD	7
9	A	1st	No	BEP/EP	1	4	NED	30+
10	A	1st	No	BOP/VIP	2	3	DOD	4
				2×VIP				
12	B	1st	Retroperitoneal	BOP/VIP	2	2	NED	25+
				3×MICE				
14	B	2nd	No	CEB	2	3	NED	21+
				4×VIP				
15	B	1st	No	EP	1	6	NED	21+
16	B	2nd	No	BEP	2	7	NED	21+
				4×VIP				
17	B	1st	No	BOP/VIP	1	3	DOD	2

BEP/EP, four courses of bleomycin, etoposide, and cisplatin, followed by two courses of etoposide and cisplatin (25); BEP, four courses of bleomycin, etoposide, and cisplatin (26); BOP/VIP, three courses of bleomycin, vincristine, and cisplatin, followed by three courses of etoposide, ifosfamide, and cisplatin (27); CE, carboplatin and etoposide; CEB, carboplatin, etoposide, and bleomycin (28); DOD, dead of disease; EP, etoposide and cisplatin (25); MICE, mesna, ifosfamide, carboplatin, and etoposide (29); NED, no evidence of disease; PR, partial remission; RFS, relapse-free survival from the start of salvage chemotherapy; TD, toxic death; UPR, unresectable partial remission; VIP, etoposide, ifosfamide and cisplatin (30).

patients (73%) were effectively salvaged by the high-dose carboplatin-based salvage protocol, 21+ to 56+ months after the start of therapy. None of these patients underwent salvage surgery. This outcome appears to be unrelated to the number of prior chemotherapy regimens (3 of 4 patients who had received more than one regimen were salvaged) or the presence of extragonadal teratoma (2 of 3 patients salvaged). Patient 4, who had a primary mediastinal mixed seminoma and teratocarcinoma, received additional radiation therapy to the mediastinum when in complete remission after the completion of the salvage regimen. Patient 12, who had a marker relapse after two lines of chemotherapy and surgery for a primary retroperitoneal choriocarcinoma, received no further treatment after the discontinuation of chemotherapy. Of the 4 patients with the earliest relapses after previous chemotherapy (2 or 3 months), 2 were not cured. Thus, a very short time since the last chemotherapy may be an adverse prognostic factor, but the number of patients is obviously too small to analyze this with any degree of confidence.

The pretreatment characteristics and outcomes for the poor-risk patients are shown in Table 3. Six of the 7 of

these patients died, resulting in a salvage rate of only 14%. The single long-term survivor is unusual in that he had only low-volume retroperitoneal lymph node metastases and progressed during first-line chemotherapy with carboplatin, etoposide, and bleomycin. He subsequently received two courses of HD-CE and responded with only a minor decrease of his tumor markers. A surgical complete remission was obtained prior to autologous bone marrow transplantation. He has been in unmaintained CR for 31+ months after the transplantation (34+ months after the start of salvage treatment).

## DISCUSSION

The prognosis of germ cell cancer patients who are not cured by adequate first-line chemotherapy with or without surgery is poor. The subgroup of patients most likely to be cured by second-line chemotherapy is that of patients relapsing from a complete remission. In this situation, chemotherapy with a cisplatin/ifosfamide-based regimen is considered standard by many clinicians. This approach leads to objective responses in 20–40% of patients, while less than half of the complete responses are durable (15).

**Table 3**  
*Pretreatment Characteristics of the "Poor-Risk" Patients*

Patient number	Part of the study	State of disease	Refractory	Extragonadal primary	Prior chemotherapy	Number of regimens	Months since last chemotherapy	Outcome	RFS (months)
3 <sup>a</sup>	A	UPR	No	No	BOP/VIP	1	1	TD	0
6 <sup>a</sup>	A	Refractory relapse	Yes	No	BEP	2	1	DOD	1
7 <sup>a</sup>	A	UPR	Yes	No	2×MICE 3×BEP	2	1	DOD	1
8	A	PR	Yes	No	3×CEB	1	1	NED	34+
11	B	UPR	Yes	Mediastinal, retroperitoneal	BEP/EP	1	2	DOD	4
13	B	UPR	Yes	Mediastinal, retroperitoneal, CNS	BOP/VIP	2	1	DOD	3
18 <sup>a</sup>	B	UPR	Yes	Mediastinal, retroperitoneal, liver	BEP EP	2	2	DOD	2

<sup>a</sup>Not transplanted

Abbreviations as in footnote to Table 2.

A retrospective review from the Memorial Sloan-Kettering Cancer Center reported a 36% salvage rate in 42 patients relapsing from a complete response (2). Similar low cure rates have been reported by others (16,17). An alternative approach consists of high-dose chemotherapy with autologous bone marrow support or with autologous peripheral stem cell reinfusion (see for recent reviews Refs. 18 and 19). Among the best results reported to date are those of Linkesch et al. (20). These investigators employed a high-dose regimen incorporating carboplatin, cyclophosphamide, and etoposide and obtained 6 CRs in 11 patients, 4 of which were durable.

Of 11 patients relapsing from CR in our study, 10 achieved a complete response, and 8 of these appear to be durable, lasting 18+ to 53+ months after transplantation or 21+ to 56+ months after the start of salvage treatment (Table 2). Although 3 of these "durable" CRs are still less than 2 years in duration, we believe that they are likely to represent long-term remissions. In our own experience, as well as in that of others (21), all relapses of germ cell cancers after transplantation occur within 6–8 months of transplantation.

The results in the poor-prognosis group, however, were certainly not better than those reported by others. Only about 15% of these patients may be salvaged with high-dose regimens (18). It was hoped that the B part of the study, which incorporated a second very-high-dose chemotherapy regimen with peripheral stem cell transplantation only 5 weeks after the previous one, would

prove to be particularly effective. The 3 poor-prognosis patients who received this treatment, however, all had cisplatin-refractory, primary extragonadal disease, which is thought to be incurable with any approach. In addition, both patients with severe toxicity from HD-CE that precluded intensive therapy with CTC and autotransplantation were also in this small group. We believe that more experience with the regimen is required to determine whether some of these patients may benefit from double transplantations.

The high-dose regimen CTC employed in this study has the advantage of causing little organ toxicity. This allows repeated administration with only brief intervals between courses, which has become possible using peripheral stem cell technology. Thus very high doses of alkylating agents can be delivered, which, extrapolating from laboratory data, may have the best prospect to eradicate resistant residual tumor cells (22). In addition, repeated high-dose chemotherapy may overcome the problem of kinetic factors that lead to a significant increase in growth fraction of the residual tumor stem cells after a single cycle of high-dose chemotherapy (23,24).

Patients with unresectable partial remissions or with cisplatin-refractory disease continue to face a very poor prognosis despite current high-dose therapy. Even further dose escalation and/or the introduction of novel drugs may be required to improve the results of salvage therapy for this patient group.

## NOTE ADDED IN PROOF

Patient number 9 relapsed 35 months after the start of salvage chemotherapy and is currently alive with disease.

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