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ORIGINAL REPORT

Sequential Versus Single High-Dose Chemotherapy in Patients With Relapsed or Refractory Germ Cell Tumors: Long-Term Results of a Prospective Randomized Trial

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ABSTRACT

Purpose
To evaluate the long-term survival rates in patients with relapsed or refractory germ cell tumors (GCTs) after single or sequential high-dose chemotherapy (HDCT).

Patients and Methods
Between November 1999 and November 2004, 211 patients with relapsed or refractory GCT were randomly assigned to treatment with either one cycle of cisplatin 100 mg/m^2, etoposide 375 mg/m^2, and ifosfamide 6 g/m^2 (VIP) plus three cycles of high-dose carboplatin 1,500 mg/m^2 and etoposide 1,500 mg/m^2 (CE, arm A) or three cycles of VIP plus one cycle of high-dose carboplatin 2,200 mg/m^2, etoposide 1,800 mg/m^2, and cyclophosphamide 6,400 mg/m^2 (CEC, arm B) followed by autologous stem-cell reinfusion. Long-term progression-free survival (PFS) and overall survival (OS) 6 years after random assignment of the last patient were compared by using the log-rank test.

Results
Overall, 108 and 103 patients were randomly assigned to arms A and B, respectivelyl. The study was stopped prematurely because of excess treatment-related mortality in arm B (14%) compared with that in arm A (4%; $P = .01$). As of December 2010, nine (5%) of 211 patients were lost to follow-up; 94 (45%) of 211 are alive and 88 (94%) of 94 patients are progression free. Five-year PFS is 47% (95% CI, 37% to 56%) in arm A and 45% (95% CI, 35% to 55%) in arm B (hazard ratio [HR], 1.16; 95% CI, 0.79 to 1.70; $P = .454$). Five-year OS is 49% (95% CI, 40% to 59%) in arm A and 39% (95% CI, 30% to 49%) in arm B (HR, 1.42; 95% CI, 0.99 to 2.05; $P = .057$).

Conclusion
Patients with relapsed or refractory GCT achieve durable long-term survival after single as well as sequential HDCT. Fewer early deaths related to toxicity translated into superior long-term OS after sequential HDCT.

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INTRODUCTION

High-dose chemotherapy (HDCT) given as first or subsequent salvage has become standard treatment for patients with relapsed or refractory germ cell tumors (GCTs) at many centers worldwide.[1,2] In the first-salvage setting, more than 70% of patients may achieve durable remissions often despite adverse prognostic factors.[1-3] Even when given second or subsequent salvage treatment, approximately 10% to 20% of patients may still be cured.[4] However, long-term follow-up data have rarely been reported, and the outcomes more than 5 years after HDCT are largely unknown.[5] The German Testicular Cancer Study Group compared two commonly used high-dose regimens in a prospective, randomized, multicenter trial. Sequential HDCT with three cycles of high-dose carboplatin and etoposide was compared with single HDCT with one cycle of high-dose carboplatin, etoposide, and cyclophosphamide as first or subsequent salvage treatment.[6] Here, we report the long-term survival of these patients with a minimum follow-up of 6 years.

PATIENTS AND METHODS

Patients and Eligibility Criteria

The trial started in September 1999 and was stopped prematurely in November 2004 after recruitment of 216 patients because of excess toxicity in arm B. Patients with

GCTs were eligible for the trial only if there was unequivocal evidence of relapse or progression after cisplatin-based combination chemotherapy for metastatic GCT as defined by either increasing tumor markers and/or progressing radiologic manifestations. Marker-negative patients needed additional histologic evidence of undifferentiated GCTs. Patients with late relapses 2 or more years after their initial treatment and patients with mediastinal primaries could be included. Details of the eligibility criteria have been previously reported.[6]

Treatment Protocol

Randomization was centrally performed and stratified according to location of the primary tumor, response to previous treatment, and number of previous cisplatin cycles. Treatment schedules in the two arms of the study were chosen according to published regimens and dosages. Treatment in arm A consisted of one cycle of conventional-dose cisplatin 20 mg/m^2, etoposide 75 mg/m^2, and ifosfamide 1.2 g/m^2 for 5 days (VIP) plus three additional cycles of high-dose carboplatin 1,500 mg/m^2 and etoposide 1,500 mg/m^2 (CE) given in three divided doses over 3 days followed by reinfusion of autologous peripheral blood progenitor cells (PBPCs) 2 days later. Cycles were to be repeated at intervals of 21 days. Treatment in arm B was identical with that in the experimental arm of the IT94 trial.[7] Patients received three identical conventional-dose cycles of VIP plus one additional cycle of high-dose carboplatin 2,200 mg/m^2, etoposide 1,800 mg/m^2, and cyclophosphamide 6,400 mg/m^2 (CEC) given in four divided doses over 4 days followed by reinfusion of autologous PBPCs 2 days later. Patients with a creatinine clearance between 70 mL/min and 100 mL/min were scheduled to receive HDCT at a reduced dose of carboplatin 1,200 mg/m^2 and etoposide 1,200 mg/m^2 in arm A, and carboplatin 1,600 mg/m^2, etoposide 1,600 mg/m^2, and cyclophosphamide 1,300 mg/m^2 in arm B. Patients with brain metastases received whole brain irradiation at a dose of 40 Gy immediately after random assignment in addition to their planned treatments.

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Clinical Evaluations and Follow-Up

Clinical evaluations included a detailed history and physical examination; conventional chest radiograms; an ECG; computed tomography scans of the brain, chest, abdomen, and pelvis; measurements of the serum tumor markers α-fetoprotein, human chorionic gonadotropin, and lactate dehydrogenase; and screening serum chemistry. Laboratory investigations were performed as required, and determinations of the tumor markers α-fetoprotein and human chorionic gonadotropin were repeated at least before each treatment cycle. Patients with a partial remission and negative tumor makers as well as patients with a partial remission and positive tumor markers were considered appropriate surgical candidates, and complete surgical resection of all residual disease was attempted.[6]

Follow-up evaluations were performed at 6 and 12 weeks post HDCT. Patients were re-evaluated every 3 months during the first year and every 6 months during subsequent years for an overall period of 3 years. Thereafter, no uniform follow-up schedule was pursued, and patients were seen at their initial referral center at the discretion of their local oncologists. To obtain long-term follow-up information on remission and survival status, questionnaires were sent and/or telephone interviews were performed at least once per year.

Statistical Analysis

Progression-free survival (PFS) was calculated from random assignment to disease progression or the date of last follow-up. Patients who died from treatment-related toxicity were censored at the time of death. Overall survival (OS) started with the date of random assignment and ended with the death of a patient from whatever cause or the date of last follow-up.

Data were analyzed by using STATA software (STATA, College Station, TX). Survival analyses were performed on an intention-to-treat basis. Survival probabilities were calculated according to the method of Kaplan and Meier.[8] The log-rank test was used to compare survival probabilities. For comparison of categorical variables, either Fisher's exact or χ^2 test was used. A difference of $P < .05$ was considered statistically significant.

Table 1. Patient Characteristics at Study Entry

Characteristic	Arm A (n = 108) No.	Arm A (n = 108) %	Arm B (n = 103) No.	Arm B (n = 103) %
Year of initial diagnosis				
Median	2000		2000	
Range	1984-2004		1983-2004	
Age, years				
Median	36		36	
Range	16-59		17-55	
Location of primary tumor				
Gonad	97	90	92	89
Retroperitoneum	8	7	8	8
Mediastinum	2	2	3	3
Other*	1	1	—	—
Histology				
Nonseminoma	84	78	84	82
Seminoma	24	22	17	16
Equivocal	—	—	2	2
Previous salvage regimens				
0	93	86	88	85
≥ 1	15	14	15	15
Prognostic groups in first salvage patients only†				
Very low risk	8	7	9	9
Low risk	18	16	14	13
Intermediate risk	42	39	37	36
High risk	18	17	19	18
Very high risk	4	4	3	3
No unequivocal classification	3	3	6	6
Late relapses (> 2 years after cisplatin-based treatment)	16	15	19	18

*One patient with a CNS primary tumor.
†Prognostic groups according to the classification of the International Prognostic Factor Study Group.[3]

RESULTS

Patient Characteristics at Study Entry

Five (3%) of 216 randomly assigned patients had to be excluded because of non-GCT histologies on data review. The characteristics of the remaining 211 patients are provided in Table 1. Known prognostic factors at study entry according to the new score of the International Prognostic Factors Study Group (IPFSG) were equally distributed between the two study arms.[3] Patients had been previously treated with a median of four cycles (range, two to nine cycles) of cisplatin-based chemotherapy; 204 (97%) of 211 patients received etoposide and 58 (27%) of 211 patients received ifosfamide during previous treatments. One hundred eighty-one (86%) of 211 patients experienced failure of first-line conventional-dose treatment, and 30 (14%) of 211 patients had recurrence after additional conventional-dose salvage regimens.

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PBPC Mobilization and Treatment

Details on peripheral PBPC mobilization and delivery of study treatments have been previously described.[6] In arm A, 19 (18%) of 108 patients discontinued their planned treatment prematurely because of progressive disease (n = 7), noncompliance (n = 3), infections

Table 2. Residual Tumor Resections

Variable	Arm A (n = 108) No.	Arm A (n = 108) %	Arm B (n = 103) No.	Arm B (n = 103) %
All residual tumor resections*	39	36	36	35
Retroperitoneum	23		16	
Lung	20		19	
Mediastinum	16		16	
Neck	1		3	
Liver	2		2	
Other	1		2	
Histology of resected specimen	39	100	36	100
Only necrosis	20	51	17	47
Vital undifferentiated cancer†	15	39	13	36
Mature teratoma	3	8	5	14
Unknown	1	2	1	3

*Patients may have had resections at multiple sites.
†Patients may have had other elements such as necrosis and/or teratoma present as well.

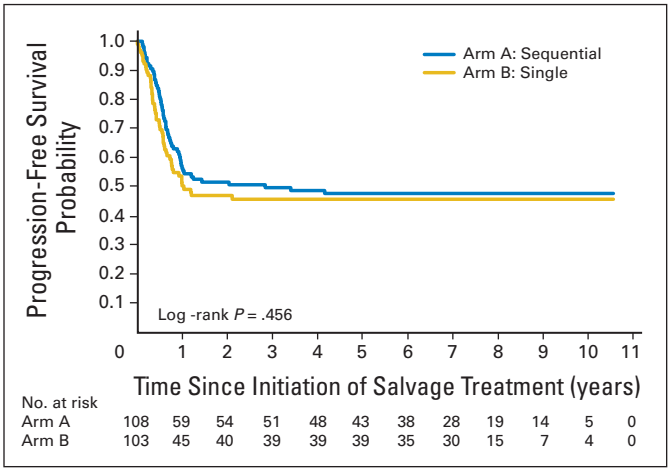

Fig 1. Progression-free survival after sequential or single high-dose chemotherapy.

(n = 2), other toxicities (n = 5), or delayed hematopoietic recovery after previous PBPC reinfusions (n = 2). Because of insufficient collection of PBPCs, 13 additional patients had to be switched from arm A to arm B. Therefore, only 76 (70%) of 108 patients completed all three high-dose CE cycles as planned, nine (12%) at reduced dosages of carboplatin and etoposide as predefined in the protocol. In arm B, 20 (19%) of 103 discontinued treatment prior to HDCT because of progressive disease (n = 10), toxicity (n = 1), treatment-related death (n = 3), noncompliance (n = 4), and other reasons (n = 2). High-dose CEC was given to only 83 (81%) of 103 patients as intended per protocol, seven (8%) of them at reduced dosages of carboplatin, etoposide, and cyclophosphamide.

Response, Residual Tumor Resections, and Survival

The maximal response rates to the salvage treatment are provided in Table 2. Residual tumor resection (RTR) after completion of HDCT was attempted whenever feasible. However, 39 patients (27 [25%] in arm A and 12 [12%] in arm B) who achieved a partial remission with negative tumor makers as their best response to HDCT did not undergo resection. The rate of successful resections was similar in arm A compared with arm B (39 [36%] of 108 patients in arm A *v* 36 [35%] of 103 patients in arm B; $P = .86$). The majority of resections were performed in the abdomen, lungs, and mediastinum. Details of the histologies in the resected specimens are given in Table 3. Among the 75 patients with RTR, 35 (47%) of 75 had resections at more than one anatomic site, of whom 13 (37%) of 35 had discrepant histologies. As of December 2010, the median follow-up time for patients still alive was 7.5 years (range, 2.5 to 10.5 years), but nine (5%) of 211 patients were lost to follow-up at 31, 32+, 36+, 47+, 47+, 51+, 55, 61+, and 71+ months, respectively. At the time of last contact, 94 (45%) of 211 patients were still alive, and 88 (42%) of 211 were free of progression; six patients who relapsed after HDCT became disease-free with third-line chemotherapy or desperation surgery, and two patients were alive with active disease. Only five relapses occurred more than 2 years after completion of salvage treatment. Overall, 117 (55%) of 211 patients died. There were 20 treatment-related early deaths, four (4%) of 108 in arm A and 16 (16%) of 103 in arm B. With further follow-up, there was one additional death from secondary acute leukemia in arm B, one patient in arm A died from a non–treatment-associated infection, and one patient in arm A died from an unknown cause. All other patients died from relapsed GCTs: 49 (45%) of 108 in arm A and 45 (44%) of 103 in arm B.

The projected PFS at 2 and 5 years did not differ between patients in either treatment arm: 52% (95% CI, 42% to 61%) and 48% (95% CI, 38% to 57%) in arm A ($P = .456$) and 47% (95% CI, 36% to 57%) and 46% (95% CI, 35% to 56%) in arm B (Fig 1). However, fewer treatment-related deaths translated into a superior

Table 3. Residual Tumor Resections, Histology of Resections, and Outcome

Localization	Without Resections	With Resections	Necrosis No.	Necrosis %	Vital Cancer No.	Vital Cancer %	Teratoma No.	Teratoma %	Missing No.	Missing %
Retroperitoneum	170	39	23	59	8	21	6	15	2	5
Lung	172	39	18	46	16	41	5	13	—	—
Mediastinum	179	32	16	50	9	28	6	19	1	3
Liver	207	4	3	75	—		—	—	1	25
Neck	207	4	—	—	2	50	2	50	—	—
Other	208	3	2	67	1	33	—	—	—	—
All patients*	136	75*								

*Among the 75 patients, 35 (47%) had resections at multiple sites.

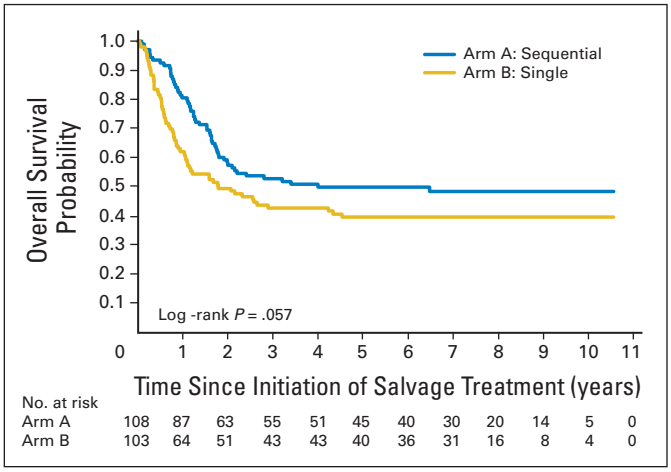

Fig 2. Overall survival after sequential or single high-dose chemotherapy.

OS in arm A at 2 and 5 years of 58% (95% CI, 48% to 66%) and 50% (95% CI, 40% to 59%) compared with arm B with 50% (95% CI, 40% to 59%) and 40% (95% CI, 30% to 49%) that was close to statistical significance ($P = .057$; Fig 2).

The projected survival rates for PFS and OS according to the different prognostic categories of patients are given in Table 4. First-salvage patients in the high-risk category as well as patients with a second salvage attempt after having relapsed from previous conventional-dose salvage treatment seemed to profit most from sequential HDCT, whereas no difference between sequential and single HDCT was observed in the best prognostic group of very-low-risk first-salvage patients. There were no long-term survivors with either salvage strategy in the worst prognostic category of very-high-risk first-salvage patients. In addition, all five patients with primary mediastinal nonseminomatous tumors eventually died from progressive disease despite prior responses in four of these patients. Patients treated for a late relapse GCT had a projected PFS at 2 years of 20% (95% CI, 9% to 34%) and a projected OS at 3 years of 32% (95% CI, 18% to 46%).

Among patients with RTR, 44 (59%) of 75 patients remained free of progression compared with 62 (46%) of 136 patients without RTR. This translated to a projected PFS at 2 years in patients with RTR of 61% (95% CI, 49% to 71%) compared with 42% (95% CI, 33% to 51%) in patients without RTR ($P < .005$). The rate of progression after resection was highly dependent on the histology of the resected specimens. Among 37 patients with necrosis and eight patients with teratoma at all resected anatomic sites, only five (14%) of 37 and three (38%) of eight progressed after surgery. This contrasts to a progression rate of 82% among 23 of 28 patients in whom vital undifferentiated cancer was detected in at least one of the resected specimens. Overall at least 10 (28%) of 26 patients with complete resection of vital undifferentiated cancer or mature teratoma became long-term survivors only after residual tumor resection.

DISCUSSION

Treatment results more than 5 years after salvage treatment have been infrequently reported in patients with GCTs.[5,9] Most investigators believe that after 2 years, relapses or progressions from complete or tumor marker–negative partial remissions are rare, and the PFS at 1 or 2 years has usually been chosen as the primary end point in previous trials. Here, we report the long-term follow-up of a prospective trial 6 years after the last patient was recruited.[6] In this trial, patients were randomly assigned to the two commonly practiced salvage strategies of sequential or single HDCT. Recruitment was stopped prematurely after inclusion of 216 patients because of excess toxicity in the single HDCT arm, but no differences in PFS or OS had been observed at the time of initial publication of the results.[6]

Several important observations can be made from the analysis of this long-term follow-up data. With a median follow-up time of more

Table 4. Survival Rates According to Prognostic Categories

Prognostic Category	No.	%	Rate of PFS at 2 Years (%)	95% CI	Rate of OS at 3 Years (%)	95% CI
First salvage: very low risk	17	8	82	55 to 94	82	55 to 94
Arm A	8	4	63	24 to 86	63	23 to 86
Arm B	9	4	100	—	100	—
First salvage: low risk	32	15	64	44 to 79	59	40 to 74
Arm A	18	9	69	40 to 86	61	35 to 79
Arm B	14	7	58	27 to 80	56	26 to 77
First salvage: intermediate risk	79	38	52	40 to 63	52	40 to 62
Arm A	42	20	51	35 to 65	55	39 to 68
Arm B	37	18	54	36 to 69	49	32 to 63
First salvage: high risk	37	18	34	19 to 50	32	18 to 47
Arm A	18	9	50	26 to 70	56	31 to 75
Arm B	19	9	14	2 to 37	11	2 to 28
First salvage: very high risk	7	3	None	—	None	—
Second or subsequent salvage	30	14	24	11 to 41	30	15 to 47
Arm A	15	7	33	12 to 56	40	17 to 63
Arm B	15	7	15	2 to 38	20	5 to 42
No unequivocal classification	9	4	76	33 to 94	67	28 to 88

NOTE. Arm A, sequential high-dose chemotherapy; arm B, single high-dose chemotherapy.
Abbreviations: OS, overall survival; PFS, progression-free survival.

than 7 years, survival rates and, hopefully, cures remain durable in a substantial proportion of patients. Overall, more than 40% of patients can be expected to be alive and to remain free of progression. This analysis confirms that relapses or progressions after 2 years are rare events and supports the concept that PFS at 2 years can be used as a surrogate marker for long-term remission or cure in patients with relapsed or refractory GCTs.

Survival rates after salvage treatment are highly dependent on the presence or absence of prognostic factors.[3,4] When we used the score recently published by the IPFSG, excellent results after salvage treatment could be demonstrated in very-low-risk first-salvage patients, with more than 80% PFS and OS probabilities. The results were substantially inferior, however, for high-risk first-salvage patients as well as for patients treated with a second salvage attempt. In these latter groups, less than one third of patients remained free of progression after 5 years or more. Unfortunately, the small group of very-high-risk first-salvage patients did not seem to profit from either of the two intensive HDCT strategies studied.

The initial analysis of the trial concluded that sequential HDCT using CE was superior to single HDCT with the addition of cyclophosphamide because of a more favorable acute toxicity profile.[6] Our analysis confirms and extends this finding. Despite an almost identical PFS probability, sequential HDCT resulted in an improved OS probability with a difference of approximately 10% at 5 years compared with single HDCT because of fewer treatment-related deaths resulting from toxicity. This effect was most prominent in the unfavorable categories of high-risk first-salvage patients and patients who experienced a second attempt at salvage. In the most extreme categories of very-low-risk first-salvage patients and very-high-risk first-salvage patients, no such difference was seen. Although the long-term survival difference in favor of sequential HDCT is based on a small number of patients and has failed to reach statistical significance, the addition of cyclophosphamide seemed to have compromised the results of standard high-dose carboplatin and etoposide, which has become the backbone of HDCT approaches in GCTs since its introduction in 1988.[10]

Resection of residual tumors has been repeatedly shown to be an integral part of any salvage strategy in patients with GCTs because the rates of vital undifferentiated tumors or teratoma after salvage treatment are substantially higher compared with other clinical scenarios.[11,12] In this series, approximately 30% of patients in each treatment arm underwent RTR with the expected high rates of vital undifferentiated tumor or mature teratoma. RTR contributed to long-term OS in approximately 28% of patients in these two groups who remained free of progression after surgery, despite the unfavorable histologies in their resected specimens, and became long-term survivors.

Two subgroups of patients deserve to be mentioned in particular. The majority of patients who relapsed or progressed after HDCT died from active cancer. Yet, six patients became permanently free of tumor with third-line chemotherapy and/or desperation surgery. This figure may be small but should serve as a reminder that expert treatment might successfully salvage individual patients, even those with multiple relapses and/or refractory disease.[5,13] Similarly, patients with late relapses more than 2 years after the last cisplatin-based chemotherapy are generally considered poor candidates for chemotherapy and are usually scheduled for desperation surgery.[14] Yet four patients with late relapses achieved a complete remission with chemotherapy alone, of whom three are alive without disease at 7+, 8+, and 8+ years. Although the optimal treatment strategy remains controversial, patients with unresectable late relapses of GCTs should therefore not routinely be excluded from HDCT.[15]

In conclusion, single HDCT using CEC as well as sequential HDCT using CE both resulted in durable long-term survival rates in relapsed and/or refractory GCTs. Sequential high-dose CE without additional cyclophosphamide, however, was better tolerated compared with single high-dose CEC and resulted in a superior OS probability at 5 years because of fewer early deaths resulting from toxicity. Long-term toxicities from either treatment have not been studied so far and should be addressed in future analyses.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

AQ: L

The author(s) indicated no potential conflicts of interest.

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AQ: M

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