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ORIGINAL ARTICLE

High-dose chemotherapy with autologous stem cell support in patients with metastatic non-seminomatous testicular cancer – a report from the Swedish Norwegian Testicular Cancer Group (SWENOTECA)

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Abstract

Background. The SWENOTECA IV protocol from 1995 is a prospective population-based study in metastatic non-seminomatous germ cell testicular cancer (NSGCT), designed for early identification of patients with poor response to standard cisplatin-based chemotherapy. A slow tumor marker decline (HCG $T_{1/2} > 3$ days, AFP $T_{1/2} > 7$ days) after BEP or BEP plus ifosfamide was regarded as poor response. The aim of this study was to present survival and toxicity data for patients treated with high-dose chemotherapy (HDCT) within the SWENOTECA IV cancer care program. *Material and methods.* In total 882 adult men diagnosed with metastatic NSGCT between July 1995 and June 2007 in Sweden and Norway (except one center) were included in SWENOTECA IV and treated accordingly. Among these, 55 men (6.2%) were treated with HDCT according to three different indications in the protocol: A) poor response to standard-dose intensified chemotherapy (BEP plus ifosfamide); B) vital cancer at surgery after intensified chemotherapy; and C) selected relapses after previous chemotherapy. In situation A and C two HDCT cycles and in situation B one HDCT cycle was recommended. Situation A was the reason for HDCT in 36 patients, B in seven and C in 12 patients. The first HDCT cycle consisted of carboplatin $28 \times (GFR + 25)$ mg, cyclofosfamide 6000 mg/m^2 and etoposide 1750 mg/m^2, administered over four days. In cycle two, etoposide was replaced by tiotepa 480 mg/m^2. *Results.* After a median follow-up of 7.5 years, overall survival was 72%, 100% and 58%, while failure-free survival was 64%, 71% and 42% in situation A, B and C, respectively. Three patients (5.5%) died during HDCT (renal failure or intracerebral hemorrhage). Nephrotoxicity was the most common non-hematological grade 4 toxicity (n = 5, 9%). *Conclusion.* The population-based SWENOTECA strategy, selecting patients who do not respond adequately to primary standard-dose chemotherapy for immediate treatment intensification with HDCT, is feasible and might be advantageous.

The majority of men with advanced germ cell tumors achieve a durable complete remission after first-line cisplatin-based chemotherapy [1]. However, 10–20% of these patients, especially those classified as "poor-prognosis" according to the International Germ Cell Consensus Classification (IGCCC), are not cured by standard cisplatin-based chemotherapy [2]. For these patients, more effective therapy is imperative. Several phase II studies, investigating the effect of first-line high-dose chemotherapy (HDCT) with stem cell support in poor-prognosis patients, have reported 2- to 5-year progression-free survival rates at 50–75% [3–6]. These studies indicate a possible survival benefit from first-line HDCT. Still, results from three randomized studies did not demonstrate superiority of HDCT over standard dose cisplatin-based

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chemotherapy [7–9]. However, these results are influenced by low dose intensity [7] or insufficient power due to early study termination [9]. The Intergroup study included 219 patients who received either four cycles of bleomycin, etoposide and cisplatin (BEP) or two BEP followed by two cycles of HDCT [8]. This study also failed to show any survival benefit for HDCT in the total patient population.

SWENOTECA (Swedish Norwegian Testicular Cancer Group) was established in 1981 to provide common national cancer care programs and clinical studies for adult testicular cancer patients. The SWENOTECA IV protocol from 1995 is a prospective population-based study in metastatic nonseminomatous germ cell testicular cancer (NSGCT), designed for early identification of patients with poor response to standard cisplatin-based chemotherapy (details reported previously) [2]. Briefly, for marker positive patients, a slow tumor marker decline (HCG $T_{1/2} > 3$ days, AFP $T_{1/2} > 7$ days) after two BEP was regarded as poor response. For marker negative patients, a $< 25\%$ reduction of the tumor volume [product of two perpendicular diameters on computed tomography (CT)] was considered a poor response. Good responders continued with BEP chemotherapy and received three or four cycles in total. For patients with poor response after two BEP, treatment was intensified with addition of ifosfamide; BEP-if (bleomycin, etoposide, cisplatin and ifosfamide) or PEI (cisplatin, etoposide and ifosfamide) (intensification step 1). For patients with poor response at the second evaluation after two cycles of BEP-if/PEI, the treatment was intensified by HDCT with stem cell support (intensification step 2). Two cycles of HDCT were recommended. Patients with retroperitoneal lymph nodes > 2 cm at initial staging underwent routinely a retroperitoneal lymph node dissection (RPLND) post-chemotherapy. Other residual tumors were resected if possible. If vital germ cell cancer was present in the pathological specimen after radical resection, one cycle of HDCT was prescribed for poor responders (previous intensification step 1).

Patients relapsing after BEP were given salvage treatment with PEI. Patients with early relapses (< 6 months) and patients with slow marker decline during salvage treatment were recommended additional treatment with two cycles of HDCT. Relapsing patients, who in their primary treatment had received BEP-if/PEI, could proceed to HDCT, provided they were still considered sensitive to cisplatin.

Accordingly, the SWENOTECA IV protocol included three groups of HDCT patients: A) poor responders to treatment intensification step 1; B) adjuvant treatment for vital cancer at surgery after intensified treatment; and C) relapses as specified above. The aim of this study was to present survival and toxicity data for patients treated with HDCT within the SWENOTECA IV cancer care program.

Methods

Patients

All adult men diagnosed with metastatic NSGCT between July 1995 and June 2007 in Sweden and Norway (except one center) were included in SWENOTECA IV. More detailed data on treatment principles and results for patients included in SWENOTECA IV 1995–2003 are recently presented [2]. Patients with extragonadal germ cell tumors or previous treatment for contralateral germ cell testicular cancer were excluded. Completeness of the SWENOTECA database was in Norway ensured by cross-checking with each treatment center's patient database, and in Sweden with the Swedish National Cancer Registry. This study was approved by the Committees for Medical Research Ethics in Norway and Sweden.

During this period, 882 patients were included in SWENOTECA IV and treated accordingly. In total 138 patients were classified as poor-prognosis. Overall 55 men (6.2%) were treated with HDCT according to three different indications in the protocol: A) patients with poor response to treatment intensification step 1 (slow marker decline, $n = 29$; progressive disease, $n = 7$; in total $n = 36$); B) patients with vital cancer at surgery after intensified chemotherapy ($n = 7$); and C) relapses as specified above ($n = 12$). Figure 1 presents treatment principles for the 43 men who received HDCT as part of the primary treatment. Furthermore, five patients included in SWENOTECA IV were treated with HDCT outside of protocol. One died of treatment, while the other four had no recurrences and were disease-free at last follow-up. These five patients are not included in the present study and are not further reported.

Harvesting of stem cells and high-dose chemotherapy

Harvesting of peripheral-blood progenitor cells (CD34 + cells) was scheduled after the first ifosfamide-containing chemotherapy cycle for all patients in the SWENOTECA protocol [2]. The minimum total number necessary for two HDCT cycles was 7×10^6 CD 34 + cells/kg. Leukapheresis and cryopreservation were performed according to each participating institution's routines.

The first HDCT cycle consisted of daily carboplatin $7 \times (\text{GFR} + 25)$ mg Day 1–4, cyclofosfamide 1500 mg/m^2 Day 1–4 and etoposide 440 mg/m^2 Day 1–4. In the second HDCT cycle given as soon as the patient had recovered, etoposide was substituted by

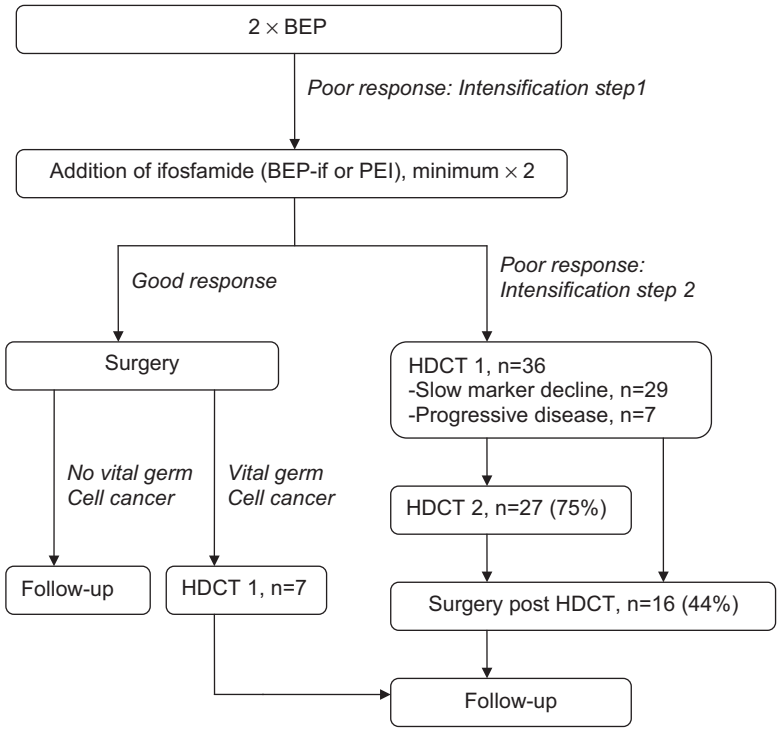

Figure 1. Principles for using high-dose chemotherapy in primary treatment. Poor response: slow tumor marker decline (HCG $T_{1/2} > 3$ days, AFP $T_{1/2} > 7$ days. BEP, bleomycin, etoposide and cisplatin; BEP-if, BEP plus ifosfamide; HDCT, high-dose chemotherapy; PEI, cisplatin, etoposide and ifosfamide.

tiotepa 120 mg/m^2 Day 1–4. Two cycles were recommended for all patients except when treatment was given in the adjuvant setting post-surgery.

Supportive care following HDCT was according to the individual institution's routines. Acute toxicity was reported and graded retrospectively according to the WHO criteria [10]. Toxicity was assessed in terms of fatal outcome, residual symptoms lasting more than a year, and normalization.

Statistics

Survival status was checked against the National Population Registries in Sweden and Norway as of June 30, 2010. The overall survival (OS), failure-free survival (FFS) and observation time were calculated from the beginning of high-dose treatment to the date of death, progression, relapse, or last follow-up. Events in the FFS included progressive disease after HDCT, relapse during follow-up and death due to treatment or progression. Survival rates were analyzed using the Kaplan-Meier method.

Univariate analyses of possible categorical predictors associated with OS and FFS were analyzed using the log rank test. Student's t-test was used to test the associations between age at HDCT and survival endpoints. Survival endpoints were also analyzed by multivariate Cox Proportional Hazard regression, presented with hazard ratios (HR) and 95% confidence intervals (CI). Due to few events, patients treated with HDCT as primary treatment and relapse were pooled together in these analyses, but the analyses were stratified for treatment indication and only three variables were included in multivariate Cox analyses [11]. The Proportional Hazard assumption was tested by visual inspection of log-log curves.

All 55 patients were included in the toxicity analyses. Patients who received HDCT as adjuvant treatment (n = 7) were excluded from survival analyses. Survival analyses are presented separately for patients who were poor responders or who received HDCT as relapse treatment. All p-values are two-sided with a significance level $< 5\%$. The data were analyzed using SPSS 17.0 (SPSS INC., Chicago, IL, USA).

Results

Patient characteristics

Fifty-five patients received HDCT according to protocol. Median follow-up was 7.5 years (range 0–14). Patient characteristics according to indication for HDCT (poor responders, adjuvant treatment or relapse) are presented in Table I. In total, 33/36

Table I. Patient characteristics according to indication for high-dose treatment (primary treatment or relapse) and for all included patients.*

Characteristic	Primary treatment, n = 43		Relapse n = 12	All patients n = 55
	Poor responders† n = 36	Adjuvant‡ n = 7		
Age at treatment, y, median (range)	29 (18–56)	25 (16–36)	36 (18–51)	28 (16–56)
Observation time, y, median (range)	7.2 (0–14.1)	10.4 (4.9–13.4)	6.6 (0–12.5)	7.5 (0–14.1)
Initial disease stage§				
Stage I Mk positive/II	1 (3)	2 (29)	2 (17)	5 (9)
Stage III	0	1 (14)	2 (17)	3 (6)
Stage IV	35 (97)	4 (57)	8 (66)	47 (85)
Initial metastatic sites				
Lymph nodes	30 (83)	7 (100)	9 (75)	46 (84)
Lung	34 (94)	4 (57)	8 (67)	46 (84)
Liver	15 (42)	0	3 (25)	18 (33)
Brain	11 (31)	0	1 (8)	12 (22)
Bone	3 (8)	1 (14)	0	4 (7)
Other‖	5 (14)	1 (14)	1 (8)	7 (13)
Marker elevation at initial diagnosis	36 (100)	7 (100)	12 (100)	56 (100)
Risk groups, initial diagnosis¶				
Good	1 (3)	1 (14)	4 (33)	6 (11)
Intermediate	2 (5)	4 (57)	2 (17)	8 (15)
Poor	33 (92)	2 (29)	6 (50)	41 (74)
Poor risk group, initial diagnosis				
Poor markers only	10 (30)	1 (50)	2 (33)	13 (32)
Extra-pulmonary metastases	23 (70)	1 (50)	4 (67)	28 (68)
Previous chemotherapy regimens				
BEP	36 (100)	7 (100)	12 (100)	55 (100)
BEP-if/PEI	36 (100)	7 (100)	12 (100)	55 (100)
EMACO	1 (2.8)	0	3 (25)	4 (7.3)
TIP	2 (5.6)	0	0	2 (3.6)
Other#	1 (2.8)	0	1 (8.3)	2 (3.6)
Chemotherapy cycles prior to HDCT, no, median (range)	5 (4–9)	6 (4–7)	9 (6–14)	5 (4–14)
Marker negative prior to HDCT	12 (33)	7 (100)	7 (58)	26 (47)

BEP, bleomycin, etoposide, cisplatin; BEP-if, BEP plus ifosfamide; EMACO, etoposide, methotrexate, dactinomycin, cyclophosphamide, vincristine; HDCT, high-dose chemotherapy; Mk, marker; no, numbers; PEI, cisplatin, etoposide, ifosfamide; TIP, paclitaxel, ifosfamide, cisplatin; y, years.

Data are numbers (%) unless otherwise specified.

†Poor responders: slow marker decline, n = 29; progressive disease, n = 7.

‡Adjuvant: vital cancer at surgery after intensified treatment.

§Staging according to the Royal Marsden Staging System.

‖Other sites of disease include skin, esophagus, small intestine, kidney and spleen.

¶According to the International Germ Cell Cancer Collaborative Group.

#One patient received oxaliplatin (poor responder) and one BEP plus paclitaxel (relapse).

patients (92%) who received HDCT due to poor response on treatment intensification step 1 were classified as poor-prognosis at initial diagnosis. All patients had been treated with BEP followed by ifosfamide-containing chemotherapy regimens. Overall median five chemotherapy cycles (range 4–14) were administered prior to HDCT.

Forty-three patients (78%) received HDCT as part of the primary treatment; 29 because of slow marker decline, seven because of progressive disease and seven due to vital cancer at post-chemotherapy surgery (Figure 1, Table II). The remaining 12 patients (22%) received HDCT as part of relapse treatment, of whom one was a late relapsing patient. Among men treated with HDCT because of poor response vs. relapse, 27/36 (75%) and 4/12 (33%) received the two intended HDCT courses, respectively. The main reasons for receiving only one course are shown in Table II. The time interval between HDCT cycle one and cycle two was median 55 days (range 30–84).

Surgical resections after HDCT among the poor responders were performed in 16 of 36 men (44%). Histological examinations revealed necrosis or fibrosis in 12 (75%) and teratoma in four patients (25%). There were no post-HDCT surgical

Table II. High-dose treatment, number of cycles. Data are numbers (%).

	Primary treatment n = 43 (78)				
	Slow marker decline n = 29 (52)	Progressive n = 7 (13)	Adjuvant n = 7 (13)	Relapse n = 12 (22)	All patients n = 55 (100)
Number of high-dose cycles					
One cycle	6 (21)	3 (43)	5 (71)	8 (67)	22 (41)
Two cycles	23 (79)	4 (57)	2 (29)*	4 (33)	33 (59)
Reasons for receiving only one high-dose cycle					
Serious toxicity†	3 (50)	1 (33)	0	3 (37.5)	7 (32)
According to the protocol	0	0	5 (71)	0	5 (23)
Progressive disease	1 (17)	1 (33)	0	2 (25)	4 (18)
Combination of serious toxicity and progressive disease	1 (17)	1 (33)	0	1 (12.5)	3 (13)
Patient refuses second cycle	1 (17)	0	0	1 (12.5)	2 (9)
Other indications (protocol violation)	0	0	0	1 (12.5)	1 (5)

*Two patients received two high-dose cycles as adjuvant treatment (protocol violation).
†Include two patients who died during the first high-dose cycle (one with the indication progressive disease and one relapse patient).

resections among men who received HDCT as relapse treatment.

Survival

HDCT due to poor response on primary treatment. OS and FFS after median 7.2 years was 72% and 64%, respectively (Table III, Figure 2), with 26/36 men being disease-free at last follow-up. Two patients (5.5%) died due to treatment-related complications, five (13.9 %) because of progressive disease and three (8.3%) due to relapse.

One patient who progressed with increasing HCG levels and pulmonary metastases after HDCT was treated with chemotherapy (PEI) and surgery. He relapsed again, and was salvaged with EMACO (etoposide, methotrexate, dactinomycin, cyclofosfamide and vincristine), and is still 11 years later in complete remission. Two of five men with relapse after HDCT achieved complete remission after salvage chemotherapy and/or surgery and were disease-free at last follow-up.

HDCT as relapse treatment. OS and FFS after median 6.6 years was 58% and 42%, respectively (Table III, Figure 2). One patient (8.3%) died because of a treatment-related complication, three of 12 (25%) died as a result of progressive disease and one patient (8.3%) died due to relapse after HDCT. Of the three patients relapsing after HDCT, two had several relapses after HDCT and were treated with salvage chemotherapy and/or surgery, and were alive with active disease at last follow-up.

Prognostic factors. Results are presented in Table IV. In univariate analyses, OS was negatively associated with age at HDCT, and men who died were older at HDCT than those who survived (mean age at HDCT 38 vs. 30 years, $p = 0.028$). OS tended to be significantly associated with marker status prior to HDCT ($p = 0.057$), but was not associated with the number of chemotherapy cycles prior to HDCT.

There was no statistically significant association between FFS and age at HDCT (mean age at HDCT 35 vs. 31 years, $p = 0.15$). FFS tended to

Table III. Outcome (survival, progression and relapse) according to indication for high-dose chemotherapy (HDCT).

	Overall survival, %	Failure-free survival, %	Progression after high-dose, %	Relapse after high-dose, %
HDCT as part of primary treatment (n = 43)				
Poor responders (n = 36)	72	64	17	14
Slow marker decline after treatment intensification (n = 29)	76	69	14	14
Progressive disease during primary treatment (n = 7)	57	43	29	14
Vital cancer at post-chemotherapy surgery (adjuvant treatment, n = 7)	100	71	0	29*
HDCT as relapse treatment (n = 12)	58	42	25	25

*Two patients treated with HDCT as adjuvant treatment relapsed after HDCT. One patient relapsed after only three months. He has had several pulmonary relapses, and has been treated with chemotherapy and surgery. He was disease-free at last follow-up. The other patient had a pulmonary relapse eleven months after HDCT. He was treated with surgery and was disease-free at last follow-up.

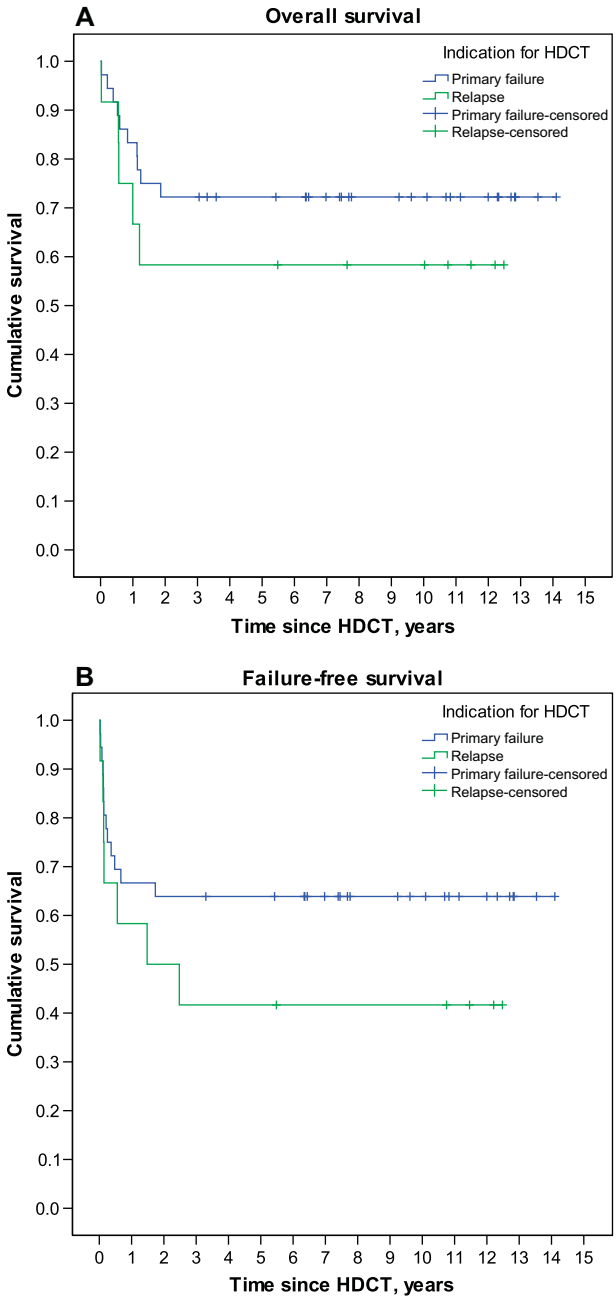

Figure 2. Survival rates for men who received high-dose chemotherapy (HDCT) due to poor response to primary treatment (BEP plus ifosfamide, n = 36) or relapse (n = 12) with overall survival rates at 72% and 58%, respectively (Figure 2A) and failure-free survival rates at 64% and 42%, respectively (Figure 2B).

be significantly associated with marker status prior to HDCT (p = 0.055), but was not associated with number of chemotherapy cycles prior to HDCT. In multiple Cox regression analyses, increasing age and being marker positive before HDCT was associated with increased risks for death or treatment failure (Table IV).

Toxicity

Treatment-related toxicity is presented in Table V. Hematologic toxicity and total ward time did not differ between the first and the second HDCT cycles. The vast majority of patients had severe mucositis and infections. Otherwise, nephrotoxicity grade 4 was the most common non-hematological toxicity, affecting 9% of all patients.

Three men (5.5%) died during HDCT at three different institutions. Two died during the first HDCT cycle, and one during the second. All were treated before the year 2000. Causes of death for these three men were: 1) renal failure and cardiac arrest (age 24 years, death during first cycle); 2) renal failure and subarachnoid hemorrhage (age 49 years, death during first cycle); and 3) intracerebral hemorrhage (age 56 years, death during second cycle).

For the remaining 52 patients, residual symptoms lasted more than a year in five (9%) patients, while the others had normal recovery of toxicity. No cases of acute leukemia have been diagnosed during follow-up.

Discussion

Herein, we have shown that HDCT for patients with metastatic NSGCT, selected as poor responders after treatment intensification according to the SWENOTECA IV cancer care program, is feasible and have resulted in favorable OS and FFS rates at 72% and 64%, respectively. No events in OS or FFS were observed after two years' follow-up for these patients. HDCT as relapse treatment resulted in notable OS and FFS rates at 58% and 42%. Patients who received HDCT as adjuvant treatment were few and thus data do not permit any conclusions. Although serious toxicity was within acceptable limits, the treatment-related mortality at 5.5% is of concern.

Strengths of this study include the prospective, population-based design, completeness of the database and the long observation period of median 7.5 years. Limitations include the relatively small sample size and the heterogeneous patient population with regard to indications for HDCT, which restrict the possibility to perform subgroup analysis.

The outcome after HDCT for poor responders to treatment intensification step 1 in the present study is superior to some of the previously published studies [4,7,9,12]. Our OS and FFS rates equal the 5-year OS and FFS rates (75% and 64%, respectively) presented by Hartmann et al. [6] and the 2-year OS rate at 71% from Motzer et al. [8]. However, both these studies included all poor-prognosis patients, while we have selected the patients with poor response to initial conventional dose chemotherapy, of whom the majority (33/36) were classified

Table IV. Univariate analyses and multivariate Cox regression analyses with HR for death or treatment failure, stratified for treatment indication (poor responders vs. relapse).*

	Death		Treatment failure	
	Univariate p-value	Multivariate HR (95% CI)	Univariate p-value	Multivariate HR (95% CI)
Age†	0.028	1.08 (1.03–1.15)	0.149	1.06 (1.01–1.11)
Mk status before HDCT	0.057		0.055	
Negative (40%)		Reference		Reference
Positive (60%)		4.60 (1.08–19.7)		5.08 (1.30–19.9)
No. of cycles prior to HDCT	0.682		0.587	1.50 (0.23–9.82)
≤4 cycles (33%)		Reference		Reference
5–6 cycles (38%)		1.31 (0.36–4.75)		1.87 (0.59–5.90)
≥7 cycles (29%)		0.50 (0.05–5.76)		1.87 (0.59–5.90)

*CI, confidence interval; HDCT, high-dose chemotherapy; HR, hazard ratio; Mk, marker; No, number.
†Age was included as a continuous variable.

as poor-prognosis. In total 138 men included in SWENOTECA IV were classified as poor-prognosis, of whom the majority received standard BEP chemotherapy alone or intensified with ifosfamide, followed by surgery in most cases.

The exclusion of men with extragonadal germ cell cancers who carry a worse prognosis than primary testicular germ cell cancers [13], may have contributed to a more favorable outcome when compared to studies where these are included. All men in our study received minimum four cycles of cisplatin-based chemotherapy prior to HDCT, which contrasts other studies where only one to two cycles of standard induction chemotherapy were administered [4,6–9,12].

Motzer et al. were the first to report promising results from the intensification strategy, with two cycles of HDCT after two conventional-dose cycles

Table V. Toxic effects of high-dose chemotherapy.*

	Primary treatment, n = 43		Relapse	All patients
	Poor responders n = 36	Adjuvant n = 7	n = 12	n = 55
Hematologic toxicity				
Days to ANC $> 1.0 \times 10^9$/L				
First cycle	10 (8–15)	9 (9–11)	10 (8–17)	10 (8–17)
Second cycle	10 (8–15)	10 (9–10)	9 (8–11)	10 (8–15)
Days to platelet count $> 20 \times 10^9$/L				
First cycle	11 (7–16)	11 (8–18)	12 (8–35)	11 (7–35)
Second cycle	11 (6–15)	11 (9–12)	10 (8–11)	11 (6–15)
Number of platelet transfusions				
First cycle	4 (0–16)	6 (4–11)	5 (2–22)	5 (0–22)
Second cycle	5 (1–12)	5 (3–6)	4 (2–7)	5 (1–12)
Total ward time				
First cycle	23 (12–37)	22 (20–28)	25 (19–54)	23 (12–54)
Second cycle	23 (13–31)	20 (19–20)	22 (17–23)	23 (13–31)
Grade 4 non-hematologic toxicity†				
Nephrotoxicity, no (%)	3 (8.3)	0	2 (16.7)	5 (9.1)
Bleeding, no (%)	3 (8.3)	0	0	3 (5.5)
Neurotoxicity, no (%)	1 (2.8)	1 (14.3)	0	2 (3.6)
Diarrhea/obstipation, no (%)	1 (2.8)	1 (14.3)	0	2 (3.6)
Cardiac toxicity, no (%)	0	0	1 (8.3)	1 (1.8)
Liver toxicity, no (%)	0	0	1 (8.3)	1 (1.8)
Pulmonary toxicity, no (%)	0	0	1 (8.3)	1 (1.8)
Treatment-related death, no (%)	2 (5.6)	0	1 (8.3)	3 (5.5)

*ANC, absolute neutrophil count; no, number.
Data are median (range) unless otherwise specified.
†According to the World Health Organization classification.

in patients with slow tumor marker decline [4,12]. Even though the Intergroup study failed to show any survival benefit for HDCT in the total patient population, a subgroup analysis of 67 patients with unsatisfactory tumor marker decline showed a significantly higher 1-year complete response rate in the HDCT treated group compared with standard BEP (61% vs. 34%, $p = 0.03$) [8]. These results support the concept that HDCT should be used for selected patients not responding sufficiently to standard-dose chemotherapy, which is in accordance with our study.

Randomized studies have been unable to demonstrate superiority for HDCT in comparison to BEP as primary treatment for poor-prognosis patients [7–9]. Nevertheless, the negative results from the French high-dose study [7] should be interpreted with caution since the dose-intensity in the HDCT arm was low and the regimen used in the control arm was not standard treatment. The EORTC study which randomized patients to four cycles of standard etoposide, ifosfamide and cisplatin (VIP) or one standard VIP cycle followed by three high-dose VIP cycles, was unfortunately closed prematurely due to slow accrual [9]. Overall survival did not differ between the two groups, but there was a tendency towards increased failure-free survival rates in favor of the high-dose VIP arm after one (66.1% vs. 48%, $p = 0.035$) and two years (58.2% vs. 44.8%, $p = 0.06$).

Several phase I/II studies [14–17] and retrospective studies [18–21] evaluating the effect of HD-CT in patients with relapse or cisplatin-refractory disease have been published. There is considerable variation in study design, patient selection and characteristics, thus FFS ranges from 35% to 63%. Our FFS rate at 42% after 6.6 years among the 12 men who received HDCT as relapse treatment is comparable to the majority of previous studies. The only published phase III study on salvage HDCT did not report any difference between treatment with standard PEI vs. one HDCT cycle (FFS 35% vs. 42%, $p = 0.16$) [22].

The treatment-related mortality rate at 5.5% in our study is comparable to some previous studies, [3,8,20,22] while others have reported lower mortality rates [9,16,19,21]. All three patients in our study died before the year 2000, and the lower later mortality rate might be a result of better supportive care after HDCT. Two of three treatment-related deaths were possibly a result of renal failure. Furthermore, nephrotoxicity grade 4 affected 9% of the patients. Renal and cardiac toxicity are known adverse effects of cyclofosfamide, particularly when applied at maximum doses as in the present study [23]. Concern has been raised regarding the increased risk for developing secondary acute leukemia after high-dose etoposide. None of our patients have developed acute leukemia, in line with the low cumulative incidence of acute leukemia at 0.5–2.6% in previous studies [24,25]. For patients who were able to receive two cycles of HDCT, toxicity in terms of hematological toxicity and in-ward time were the same for the first and the second cycle.

A single HDCT cycle is probably inadequate to provide optimal cell kill as indicated by results presented by Pico et al. [22]. SWENOTECA has recommended tandem cycles, in line with the majority of other studies. Some have included triplet HDCT, but these studies have used lower dosages of the active drugs and less pretreatment [15,17]. No conclusions can be made with regard to the optimal number of HDCT cycles from the present study, as this question not was an aim of the study protocol. Increasing age at HDCT and being marker positive before HDCT were unfavorable prognostic factors for survival in our study.

In conclusion, we have shown that the SWENOTECA HDCT strategy is a feasible approach within a population-based cancer care program. Selecting patients who do not respond adequately to primary standard-dose chemotherapy, for immediate treatment intensification with HDCT, might be advantageous. By this strategy, HDCT was limited to only 6% of patients initially presenting with metastatic disease. Future studies should aim for an optimal selection of the patients who will benefit from HDCT.

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Supplementary material available online

Appendix at http://informahealthcare.com/doi/abs/10.3109/0284186X.2011.641507.