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Original Paper

High-dose Chemotherapy in Germ Cell Tumours: a Large Single Centre Experience

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High-dose chemotherapy (HDCT) has evolved as a strategy to improve the treatment outcome in patients with relapsed and/or refractory germ cell tumours. Between August 1989 and September 1995, 150 consecutive patients with relapsed and/or refractory germ cell tumours were treated with conventional-dose salvage chemotherapy followed by one cycle of HDCT with carboplatin 1500–2000 mg/m^2, etoposide 1200–2400 mg/m^2 and ifosfamide 0–10 g/m^2 and were retrospectively analysed. With a median follow-up time of 55 months (range 21–88 months) 51/150 (34%) patients are alive and disease free. The projected event-free and overall survival are 29% (confidence interval 22–37%) and 39% (confidence interval 31–47%) respectively. The relevance of prognostic variables for long-term survival after HDCT were prospectively confirmed. Persisting toxicities occurred in approximately one third of the long-term survivors. Treatment intensification with HDCT resulted in a significant proportion of long-term survivors in patients with relapsed and/or refractory germ cell tumours. Trials to prospectively evaluate HDCT as an early intervention in these patients seem justified. © **1998 Elsevier Science Ltd. All rights reserved.**

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INTRODUCTION

More than 80% of patients with metastatic germ cell tumours will be cured by first-line combination chemotherapy plus surgical resection of residual tumour [1]. The outcome is considerably worse, however, for patients with 'poor risk' features at initial diagnosis, for those who relapse or progress after a favourable initial response and for those who become refractory to cisplatin. Although the response rate to salvage treatment has been reported to be as high as 60%, subsequent relapses are frequent and overall only 15–30% of patients will become long-term survivors [1–6]. High-dose chemotherapy (HDCT) followed by re-infusion of progenitor cells either from bone marrow (BM) or peripheral blood might be a more efficient alternative to conventional-dose salvage treatment [7–15].

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We performed the present analysis to re-evaluate and to extend our experience with HDCT as intensification of first-line or as first or subsequent salvage treatment in a large cohort of patients included in consecutive clinical trials since 1989.

PATIENTS AND METHODS

Patients

Between August 1989 and September 1995 we treated 150 patients with either relapsed or refractory germ cell tumours in consecutive clinical trials with high-dose carboplatin, etoposide and ifosfamide followed by autologous stem cell reinfusion (ASCR). Details on the individual trials have been previously reported [12, 16–19].

There were 2 female and 148 male patients with a median age of 31 years (range 18–55 years). 1 female had a mediastinal primary germ cell tumour, the other female had gestational choriocarcinoma. Among the male patients, 119 (80%) had a gonadal primary tumour; 22 (15%) had primary retroperitoneal tumours with or without additional mediastinal

involvement and 7 (5%) patients had primary mediastinal tumours. The initial histology was pure seminoma in 12 (8%) patients, the other 138 (92%) patients had non-seminoma or mixed histologies.

The reason for inclusion into one of several consecutive HDCT trials was the intensification of first-line treatment in 13 (9%) patients with poor risk features at initial diagnosis and an inappropriate or delayed response after the first few treatment cycles; 95 (63%) patients with relapsed or progressive disease were included for intensification of their first salvage treatment and 42 (28%) patients were included for intensification of their second or subsequent salvage attempt. At the time of study entry all patients had received cisplatin-based conventional-dose chemotherapy with a median of five (range 2–11) cisplatin containing cycles corresponding to a median of two (range 1–4) cisplatin-based treatment regimens; 144/150 (96%) patients had been treated with etoposide and 90/150 (60%) patients with ifosfamide. Entering the studies, 2 (1%) patients were in tumour marker-negative partial remission (PRm −), 28 (19%) patients were in tumour marker-positive partial remission (PRm +), and 120 (80%) patients had progressive disease (PD). The sensitivity to cisplatin at study entry was judged as sensitive in 119 (79%) patients, as refractory in 25 (17%) patients and as absolute refractory in 6 (4%) patients (see Definitions).

In order to re-assess the sensitivity to conventional-dose salvage treatment and to maintain tumour control until HDCT could be given, the patients were scheduled to receive further conventional-dose chemotherapy as salvage treatment immediately prior to HDCT using cisplatin 100 mg/m^2, etoposide 500 mg/m^2 and ifosfamide 6.0 g/m^2 for a median of two (range 1–3) treatment cycles. Details of the response to conventional-dose salvage treatment and the patient characteristics immediately prior to HDCT are shown in Tables 1 and 2. Among 6 patients with 'absolute refractory' disease at study entry, 1 patient was still considered absolutely refractory prior to HDCT, 3 patients were refractory and showed disease progression after a transient response and 2 patients were found to have sensitive tumours. Similarly, among 25 patients considered to be 'refractory' to cisplatin at study entry, 5 patients proved to be absolutely refractory after conventional-dose study treatment, 11 patients remained refractory and achieved only stable disease (SD) or PD prior to HDCT and 9 patients were considered sensitive prior to HDCT. Among 119 'sensitive' patients at study entry, 6 patients turned out to be absolutely refractory, 23 patients turned out to be refractory with SD or PD prior to HDCT and 90 patients remained sensitive to conventional-dose study treatment prior to HDCT. However, 6 of the latter patients had evidence of disease progression prior to HDCT despite having favourably responded to the conventional-dose study treatment. The remission status prior to HDCT in relation to the cisplatin sensitivity at study entry is shown in Table 2.

Table 1. *Patient characteristics prior to high-dose chemotherapy (HDCT)*

	Number of patients (%)
All patients	150 (100)
Location of primary tumour	
Testis	119 (80)
Retroperitoneum ± mediastinum	23 (15)
Mediastinum	8 (5)
Reason for HDCT	
Intensification first-line treatment	13 (9)
Intensification first salvage treatment	95 (63)
> first salvage treatment	42 (28)
Sensitivity to cisplatin	
Sensitive	101 (67)
Refractory	37 (25)
Absolute refractory	12 (8)
Level of HCG (in U/l)	
< 10 (normal)	103 (69)
< 1,000	35 (23)
≥ 1,000	12 (8)
Level of AFP (in ng/ml)	
< 10 (normal)	111 (74)
< 1,000	30 (20)
≥ 1,000	9 (6)
Risk categories for HDCT (according to [17])	
Score 0 ('good risk')	92 (61)
Score 1 or 2 ('intermediate risk')	37 (25)
Score > 2 ('poor risk')	21 (14)

HCG, human chorioaic gonadotrophin, AFP, alpha-feto protein.

Treatment

Details of the HDCT and the supportive care have been reported previously [12, 16, 19]. In the initial 54 patients, HDCT was administered using stepwise escalating doses of carboplatin 1,500–2,000 mg/m^2, etoposide 1,200–2,400 mg/m^2, and ifosfamide 0–10 g/m^2. After the maximally tolerated dose level was determined, 96 additional patients received a fixed combination of carboplatin 1,500 mg/m^2, etoposide 2,400 mg/m^2, and ifosfamide 10 g/m^2 [12]. Carboplatin and etoposide were administered as short infusions over 1 h in divided doses over 3–4 days. Ifosfamide was given as a continuous infusion over 22 h in divided doses over 4 days. Mesna and hyperhydration were used for uroprotection in all patients. No a priori adjustments in the carboplatin dose according to a patient's renal function were made. However, in patients who experienced severe cutaneous, renal or central nervous toxicity during HDCT, reductions in the dosages of all drugs were made as previously described [19]. Usually, the fourth treatment day was omitted in these patients. BM was used as stem cell rescue in 69 (46%) patients, peripheral blood progenitor cells (PBPC) in 75 (50%) patients and a combination of both in an additional 6 (4%) patients. In

Table 2. *Efficacy of the conventional-dose salvage treatment prior to high-dose chemotherapy (HDCT) in relation to the reported sensitivity to cisplatin at study entry*

	Response status prior to HDCT				
Response status at study entry	CR *n*	PRm − *n*	PRm + *n*	SD *n*	PD *n*
Sensitive* ($n = 119$)	11	40	33	10	25
Refractory* ($n = 25$)	0	4	5	2	14
Absolutely refractory* ($n = 6$)	0	1	1	0	4
All ($n = 150$)	11	45	39	12	43

*Reported sensitivity to cisplatin by referring hospitals. CR, complete remission; PRm −, tumour marker-negative partial remission; PRm +, tumour marker-positive partial remission, SD, stable disease; PD, progressive disease.

patients with residual lesions after HDCT, complete surgical resection was attempted whenever possible.

Follow-up

Routine follow-up evaluations were performed at 6 and 12 weeks post-HDCT and consisted of a detailed physical examination, clinical neurological assessments, computerised tomography (CT) scans of involved body regions, standard chemistry profiles, as well as of measurements of HCG and AFP levels. Additional investigations were performed as clinically indicated. Thereafter, patients were re-evaluated every 3 months during the first year and every 6 months during subsequent years. Consecutive patients treated between August 1989 and September 1995 are included in the present analysis and re-assessed as of April 1997. 1 patient was lost to follow-up at 9 months after HDCT and censored at the day of the last follow-up.

Definitions

Patients with complete disappearance of all tumour lesions including marker normalisation with chemotherapy alone were classified as complete remissions (CR). If patients became free of disease only after additional resection of necrosis or mature teratoma they were considered a 'pathological complete remission' (pCR) and if viable undifferentiated tumour elements could be demonstrated, a 'surgical complete remission' (sCR). Patients with radiological residual disease or incomplete resection of residual disease, but normal tumour markers were considered PRm − ; a PRm + required a decline of tumour markers for a minimum of 12 weeks post-HDCT. All patients with a lesser response either had SD or PD as their best response after HDCT.

Tumour sensitivity to cisplatin was classified according to the response after the last cisplatin-based chemotherapy before HDCT. Any disease was considered sensitive to cisplatin when more than SD was achieved and no evidence of tumour progression was observed within 4 weeks. The tumour was classified refractory to cisplatin when at least SD or better was achieved, but with evidence of tumour progression within 4 weeks after the last cisplatin-based chemotherapy. The tumour was absolutely refractory to cisplatin when progression was observed during the cisplatin-based chemotherapy.

Statistical analysis

Survival probabilities for failure-free and overall survival were calculated according to the method of Kaplan and Meier and compared using the log rank test [20, 21]. The overall survival time was measured from the date of stem cell re-infusion to the date of death or April 1997. The failure-free survival time was calculated from the date of stem cell re-infusion until the date of treatment failure as defined by disease progression, relapse or death from any cause, whichever occurred first. Patients without a treatment failure were censored as of April 1997. Calculations were performed on a personal computer using the PRISM statistical software (GraphPad Software Inc., San Diego, California, U.S.A.). Survival curves were compared with the log rank test.

RESULTS

Maximal treatment response

All patients received conventional-dose salvage treatment immediately prior to HDCT. The patient and disease characteristics immediately prior to HDCT are shown in Table 1. By this approach, tumour control could be achieved in 107 (71%) patients; 43 (29%) patients did not respond to conventional-dose salvage treatment immediately prior to HDCT or showed disease progression after a transient response (Table 2). The response to HDCT was evaluated 6 and 12 weeks after stem cell re-infusion at which time decisions about additional surgery were made. A CR to HDCT alone was achieved in 12/150 (8%) patients and additional surgery resulted in complete resection of residual masses in a further 29/150 (19%) patients with a PRm − as well as in 8/150 (5%) patients with PRm + after HDCT for an overall CR/NED rate of 49/150 (33%). PRm − as their best response after HDCT was achieved by 38/150 (25%) patients, who either had unresectable residual lesions or who declined surgery. Among 24/150 (16%) patients with PRm + to HDCT alone, 8 of the aforementioned patients with only minimally elevated markers after HDCT had complete resection of residual tumour with postoperative marker normalisation. The remaining 16 patients with PRm + had only a transient marker decline and progressed after HDCT, and 42/150 (28%) patients had no response or PD after HDCT. Toxic deaths due to treatment related complications occurred in 5/150 (3%) patients.

With a median follow-up time of 55 months (range 21–88 months) 60/150 (40%) patients are alive and, of these, 45/150 (30%) patients are living without treatment failure. Further salvage attempts in 58 patients who relapsed or progressed after HDCT were successful in 6/58 (10%). In these 6 patients various strategies including further HDCT, daily oral etoposide treatment, or surgery with or without additional radiation resulted in ongoing CR. Therefore, at the time of last response evaluation 51/150 (34%) patients were known to be disease-free or in durable PRm − and a further 9/150 (6%) patients were still alive with active disease. Only 1 patient was lost to follow-up in PRm − 9 months after HDCT. The remaining 89 patients died either from treatment related acute toxicity or from disease progression after HDCT except 1 patient, who had relapsed 3 months after HDCT and developed secondary acute myeloid leukaemia 1 year after HDCT having received oral etoposide intermittently as palliative treatment. The projected overall survival and failure-free survival rates for all 150 patients are shown in Figure 1. The projected event-free and overall

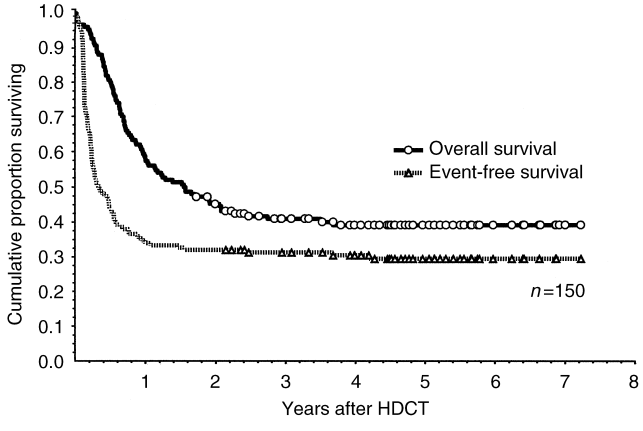

Figure 1. Projected event-free and overall survival rates. Patients alive are indicated as (○), patients without event after high-dose chemotherapy (HDCT) are indicated as (△).

survival are 29% (confidence interval (CI) 22–37%) and 39% (CI 31–47%) respectively.

Prognostic factors for treatment response

In a previous multivariate analysis on 283 patients from four different institutions, uncontrolled disease at the time of HDCT, refractory and absolute refractory disease to conventional-dose cisplatin as well as high levels of HCG prior to HDCT independently related to an inferior survival after HDCT [17]. Categories of 'good risk', 'intermediate risk' and 'poor risk' for a failure-free survival at 2 years after HDCT could be derived from a prognostic score based on these variables. As only 104 patients treated up to July 1993 were included from our institution in this previous analysis, we prospectively tested the predictive power of the prognostic score in 46 consecutive patients treated in an identical manner from July 1993 until September 1995. Although the survival rates in these latter 46 patients were worse as compared with our previous cohort, the prognostic score still identified the same three categories of 'good risk', 'intermediate risk' and 'poor risk' patients with significantly different failure-free and overall survival rates. Among these most recently treated patients, 29 'good risk' patients had a projected overall survival rate at 2 years of 51% (CI 32–70%). This contrasts with a projected overall survival of 25% (CI 0–50%) in 12 'intermediate risk' patients. Among the 5 'poor risk' patients there were no long-term survivors and their median overall survival was only 77 days (CI 8–146 days) ($P < 0.05$ for all comparisons and for trend). The Kaplan–Meier plots for overall survival according to the prognostic score are shown in Figure 2.

Unlike in our previous multicentre analysis, the timing of HDCT remained an important independent prognostic factor in the 150 patients treated at our institution, which was particularly helpful to subdivide further the large group of 92 'good risk' patients. Among the 'good risk' patients, the projected overall survival rates at 2 years were 78% (CI 50–100%), 66% (CI 53–78%) and 47% (CI 27–68%) depending on whether HDCT was used as first-line, first salvage or subsequent salvage treatment, respectively ($P < 0.05$ for comparisons between groups and for trend).

Toxicities

As expected all patients experienced severe haematological toxicity grade IV according to WHO criteria, but all showed

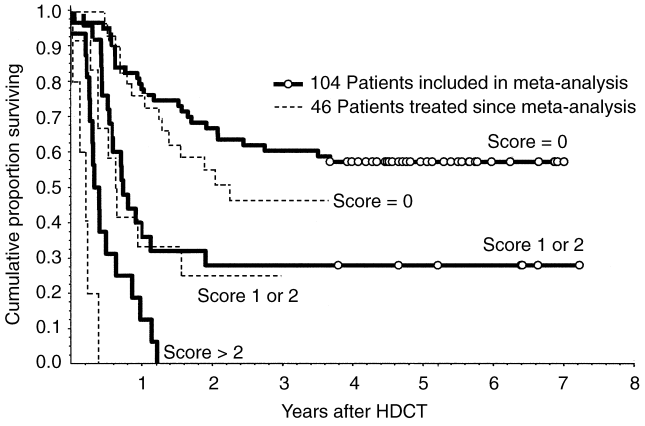

Figure 2. Projected overall survival rates according to prognostic scores (according to [17]. Patients alive are indicated (○=included in retrospective multivariate analysis; - - - =included in prospective evaluation).

complete haematological recovery after stem cell re-infusion. The use of PBPC plus a haematopoietic growth factor with or without additional BM in 76 patients resulted in a significantly faster recovery of leucocytes (10 versus 13 days, $P < 0.001$), of neutrophils (10 versus 13 days, $P < 0.001$) and platelets (11 versus 18 days, $P < 0.001$) as compared with 49 patients who received BM plus growth factor support as stem cell rescue. This translated into less transfusions of red blood cells (6 versus 9 units, $P < 0.001$) and platelets (5 versus 7.5 units, $P < 0.001$) and a shorter hospital stay (17 versus 23.5 days, $P < 0.001$) after stem cell re-infusion in patients with PBPC plus a haematopoietic growth factor as compared with patients with BM plus a haematopoietic growth factor. Nephrotoxicity in 43/150 (29%) patients and central nervous toxicity WHO grade 2 or more in 21/150 (14%) represented the dose-limiting toxicities with this HDCT combination. Overall, 12/145 (8%) required haemodialysis, of whom 10 patients recovered with their renal function until discharge. The incidence of acute nephrotoxicity and its implications for the clinical course after HDCT have been reported in greater detail elsewhere [19]. The other immediate non-haematological organ toxicities are listed in Table 3.

With a median follow-up of 55 months (range 21–93 months) 1 patient developed secondary acute myeloid leukaemia, but there were other relevant late organ toxicities

Table 3. *Spectrum of immediate organ toxicities after high-dose chemotherapy (HDCT)*

Toxicity	None	Grade 1 (*n*)	Grade 2 (*n*)	Grade 3 (*n*)	Grade 4 (*n*)	Total* (*n*)
Vomiting	0	0	8	37	100	145
Mucositis	1	4	16	45	80	145
Diarrhoea	18	38	65	24	0	145
Liver	20	55	48	21	1	145
Lung	121	18	1	5	0	145
Cystitis	96	39	8	2	0	145
Heart	134	6	5	0	0	145
Skin	60	48	33	4	0	145
PNS	51	48	41	5	0	145
CNS	105	22	11	7	0	145
Ototoxicity	77	23	37	8	0	145

*5 additional patients died from treatment related toxicities and are not included in this table: 3 patients died from severe nephrotoxicity and CNS toxicity with or without multi-organ failure, and 2 patients died from pneumonia, sepsis and consecutive multi-organ failure. PNS, peripheral nervous system; CNS, central nervous system.

Table 4. Spectrum of late organ toxicities after high-dose chemotherapy (HDCT) in long-term survivors

	Immediately after HDCT					
	All patients ($n = 150$) (%)	Long-term survivors ($n = 60$) (%)	Last follow-up Long-term survivors ($n = 60$)			
Maximum creatinine (mg/dl)			< 1.5	1.5–1.99	2.0–2.99	Dialysis
< 1.5	81 (54)	34 (57)	31	3	–	–
1.5–1.99	36 (24)	14 (23)	14	–	–	–
2.0–2.99	12 (8)	3 (5)	–	2	1	–
> 3.0	12 (8)	5 (8)	–	3	2	–
Dialysis	9 (6)	4 (7)	1	1	1	1
PNS* toxicity	94 (63)	44 (73)	23 (38%)			
Ototoxicity†	68 (45)	25 (42)	16 (27%)			
Other toxicities‡	1 (1)	1 (2)	4 (7%)			

*Polyneuropathy. †Hearing impairment and/or tinnitus; ‡Hepatitis B and/or C infection; aseptic necrosis of the right femoral head.

among the 60 long-term survivors (Table 4). At the time of last evaluation impaired renal function was documented in 14/60 (23%) patients and peripheral nervous toxicity that interfered with their daily lives was reported by 23/60 (38%) patients. Ototoxicity with tinnitus and subjective hearing loss was reported by 16/60 (27%) patients, although hearing aids were not required in any of them (Table 4). One patient developed an aseptic necrosis of his right femoral head that was treated with hip replacement surgery and 3 patients contracted a transfusion related hepatitis.

DISCUSSION

Since the introduction of high-dose carboplatin and etoposide with or without additional ifosfamide or cyclophosphamide into the salvage treatment of patients with relapsed and/or refractory germ cell tumours, response rates of 44–65% and long-term failure-free survival rates of 12–39% have been reported from various centres [7–15, 17, 18]. These results compare favourably to the ones observed after conventional-dose salvage treatment, although no prospective randomised studies have been completed to prove any superiority of HDCT [2–6]. Unfortunately, most trials that investigated either conventional-dose or high-dose salvage treatment have been similarly limited by the small number of patients included as well as by heterogeneity of the respective patient populations and treatment schedules. In the present analysis we report our experience in a large series of 150 patients with relapsed and/or refractory germ cell tumours treated in an identical manner in consecutive protocols with conventional-dose salvage chemotherapy followed by one cycle of high-dose carboplatin, etoposide and ifosfamide.

The 33% overall CR/NED rate in the present analysis and a projected long-term overall survival of 39% are encouraging and clearly demonstrate the activity of the strategy of using conventional-dose salvage treatment first followed by subsequent HDCT in patients with relapsed and/or refractory germ cell tumours. Conventional-dose salvage treatment effectively halted disease progression and resulted in tumour control priority to HDCT in approximately two thirds of patients. Moreover, it allowed the sensitivity of the tumours to be tested which turned out to be one of the strongest predictive factors for response to subsequent HDCT and long-term survival. Conventional-dose salvage treatment prior to HDCT also permitted the collection of large numbers of progenitor cells from the peripheral blood which eventually replaced BM as their primary source [16]. Indeed, the present analysis confirms that rescue with PBPC results in a significantly faster trilineage recovery, in less transfusion requirements and a shorter hospital stay as compared with BM rescue. Several issues on the use of HDCT in germ cell tumours, however, remain unsolved.

Early as well as the late toxicities after HDCT are substantial. Although the treatment related mortality was considerably lower compared with reports that pioneered this treatment, it remained constantly around 3% in consecutive protocols at our centre. Apart from the expected haematological toxicity that resulted in transfusion requirements in all patients, the majority of patients also experienced severe mucositis that necessitated hospitalisation, total parenteral nutrition and intravenous analgesia. Other non-haematological toxicities that eventually became dose-limiting were renal impairment as well as central and peripheral nervous toxicity. The use of ifosfamide as a third drug in addition to high-dose carboplatin and etoposide might have precipitated these toxicities. Despite the activity of ifosfamide in germ cell tumours at conventional doses, only modest dose increments were possible in the present combination. Alternative HDCT schedules without ifosfamide are, therefore, being investigated.

Whereas most of the acute toxicities were reversible, approximately one third of patients reported persisting side-effects, mainly paresthesias and/or tinnitus, that interfered with their daily activities. Long-term toxicities have also been reported after conventional-dose cisplatin-based treatment, but persisting side-effects as well as more severe late toxicities such as renal impairment, transfusion related hepatitis and etoposide-induced secondary leukaemia clearly act as a reminder to use HDCT judiciously, preferably only within clinical trials and at experienced centres [18, 22, 23].

To direct resources to those patients who are likely to benefit most and to avoid unnecessary toxicity in patients in whom a benefit seems very unlikely, prognostic factors for treatment outcome after HDCT were evaluated in a large retrospective analysis of 283 patients treated with HDCT at four centres in the U.S.A. and Europe [17]. A non-seminomatous primary mediastinal tumour, PD at the time of HDCT, high levels of HCG and increasing degrees of refractoriness to cisplatin-based conventional-dose treatment all independently related to an inferior treatment outcome after HDCT. In the present analysis we prospectively evaluated the prognostic score that was derived from these variables in 46 patients treated since our initial report. Although the survival rates in each of the prognostic groups were lower

in these most recently treated patients, the prognostic model still separated three groups of patients with significantly different survival. In particular, all patients within the 'poor risk' category died shortly after HDCT and should no longer be considered candidates for such treatment. New phase I or II studies to evaluate alternative treatment strategies for these patients are urgently needed. Controversies remain whether HDCT should be used as early treatment intensification or limited to patients with multiple relapses of undifferentiated tumour in whom conventional-dose chemotherapy or 'desperation' surgery is rarely curative. Two large randomised trials are currently comparing HDCT with conventional-dose first-line and first salvage treatment, respectively, and the results of these trials will have to be awaited before the optimal timing of HDCT can be determined. The present analysis included a heterogenous population in respect to the timing of HDCT and might have been biased towards more favourable results as 13 patients received HDCT as intensification of first-line treatment. Indeed, the survival rates in 'good risk' patients declined significantly depending on whether HDCT was used as first-line, first salvage or subsequent salvage treatment. This trend did not reach statistical significance in patients with an 'intermediate risk' score and could no longer be determined in 'poor risk' patients, possibly because of the small numbers of patients in each group. Whereas this finding does not justify early intervention with HDCT outside clinical trials and might represent an overtreatment in some patients, it supports the concept of investigating HDCT as early treatment intensification within clinical trials and to prospectively compare it with conventional-dose chemotherapy.

Current approaches to improve the results of HDCT in germ cells tumours are aimed at increasing its efficacy through the incorporation of new and hopefully more powerful drugs or through the administration of repetitive HDCT cycles and attempt to reduce further the toxicity of the procedure. Whereas these trials are important to optimise the application of HDCT, it seems to be difficult at the present time to perceive substantial increases in response or survival rates beyond what has been achieved with currently available HDCT strategies so far.

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