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Analysis of salvage treatments for germ cell cancer patients who have relapsed after primary high-dose chemotherapy plus autologous stem cell support

C. Kollmannsberger[a], N. Schleucher[b], O. Rick[c], B. Metzner[d], J.T. Hartmann[a], P. Schöffski[e], J. Beyer[f], J. Casper[g], M. Sosada[h], H.-J. Schmoll[i], I. Böhlke[a], C. Meisner[j], L. Kanz[a], C. Bokemeyer[a,*]

[a]*Department of Hematology/Oncology, University of Tuebingen, Otfried-Mueller-Str. 10, 72076 Tuebingen, Germany*
[b]*Department of Hematology/Oncology, Westdeutsches Tumorzentrum Essen, Hufelandstr. 55, 45122 Essen, Germany*
[c]*Department of Hematology/Oncology, Charite-University of Berlin, Schumannstr. 21, 10117 Berlin, Germany*
[d]*Department of Hematology/Oncology, Kliniken Oldenburg, Dr. Eben-Str. 10, 26133 Oldenburg, Germany*
[e]*Department of Hematology/Oncology, University of Hannover Medical School, Karl-Neuberg-Str. 1, 30625 Hannover, Germany*
[f]*Department of Hematology/Oncology, University of Marburg, Baldingerstr., 35033 Marburg, Germany*
[g]*Department of Hematology/Oncology, University of Rostock, Postfach 10888, 18057 Rostock, Germany*
[h]*Department of Hematology/Oncology, Siloah-KH Hannover, Rosebeckstr. 15, 30449 Hannover, Germany*
[i]*Department of Hematology/Oncology, University of Halle; Ernst-Grube-Str. 40, 06120 Halle/Saale, Germany*
[j]*Institute for Medical Information Processing, University of Tuebingen, Westbahnhofstr. 55, 72070 Tuebingen, Germany*

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Abstract

The aim of this study was to identify treatment strategies and therapeutic or clinical factors that predict for response to salvage therapy and survival in patients with metastatic 'Indiana advanced' or International Germ-Cell Cancer Collaborative Group (IGCCCG) poor prognosis' germ cell cancer (GCT) failing first-line sequential high-dose chemotherapy plus autologous stem cell support (HD-CT). A total of 58 'poor prognosis' patients who had relapsed after HD-CT were identified within two large prospective German first-line HD-CT trials ($n=286$) performed between March 1993 and March 2001. Salvage treatment consisted of the following: cisplatin-based conventional dose CTx ± resection (19/58; 33%), non-cisplatin based CTx (16/58; 28%) or salvage HD-CT (14/58; 24%) ± resection; resection ($n=3$) and/or radiation ($n=5$) only: 7 patients (12%); no specific therapy: 2 patients. 21 (38%) patients responded favourably (Complete Response (CR)/Partial Response (PR) marker–negative) to salvage therapy. The use of salvage HD-CT (2-year survival 48%; $P=0.03$, the complete resection of residual masses (2-year survival 42%; $P=0.015$) as well as a favourable response to salvage therapy (2-year survival: 31%, $P=0.014$) were the only variables on univariate analysis associated with an improved survival. The estimated 2-year overall survival rate is 32% (95% Confidence Interval CI: 29–45%). Approximately 30% of patients relapsing after first-line HD-CT will survive > 2 years, particularly those patients who can be treated with a second HD-CT + and/or surgical resection. If feasible, complete surgical resection of residual tumours appears to be the most efficient treatment.

Keywords: Germ cell cancer; High-dose chemotherapy; Relapse; Salvage therapy; Prognostic factors

1. Introduction

Today, approximately 70–80% of patients with metastatic germ cell cancer (GCT) can be cured by cisplatin-based combination chemotherapy [1,2]. However, patients with advanced metastatic disease fulfilling the International Germ-Cell Cancer Collaborative Group (IGCCCG) 'poor prognosis' criteria only achieve long-term survival rates of 45–50% after standard-dose chemotherapy [3]. High-dose chemotherapy followed by autologous peripheral blood stem cell (PBSCT) or autologous bone marrow support (HD-CT/PBSCT) has been increasingly investigated in this group

* Corresponding author. Tel.: +49-7071-298-4477; fax: +49-7071-293675.
E-mail address: carsten.bokemeyer@med.ui-tuebingen.de (C. Bokemeyer).

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of patients in order to improve survival rates [4–6]. Several phase II studies have consistently reported promising 2-year survival rates of approximately 70–80% indicating that a 15–20% survival advantage may be achievable with first-line HD-CT/PBSCT compared with standard-cisplatin, bleomycin, etoposide (PEB) therapy [4,6–9]. This hypothesis was recently further supported by a large multivariate and matched-pair analysis including 456 patients, 147 of whom had been treated with HD-CT/PBSCT and 309 with standard PEB or VIP (etoposide, ifosfamide, cisplatin) chemotherapy [10]. Both progression-free (75% versus 59%) and overall survival rates (82% versus 71%) were significantly better for patients receiving first-line HD-CT/PBSCT. Two prospective randomised phase III trials in the US and in Europe are currently testing the value of HD-CT/PBSCT as first-line treatment for patients with IGCCCG poor or intermediate prognosis disease.

Based on data from the phase II studies referred to above, 20–30% of patients will still relapse despite first-line HD-CT/PBSCT. For these patients, no therapeutic strategies have as yet been systematically explored and no standard treatment has been defined. The feasibility of different salvage strategies or predictive factors for response and survival for patients relapsing after first-line HD-CT/PBSCT are not known. Considering the increasing number of patients treated with first-line HD-CT/PBSCT, we conducted a retrospective analysis of all relapsed patients among 286 consecutively treated patients from two prospective first-line HD-CT/PBSCT trials of the German Testicular Cancer Study Group [6,9]. The aim of this analysis was to describe the salvage treatment strategies used as well as to characterise the overall outcome of these patients. In addition, we explored possible clinical factors that may predict for response and survival after failure from first-line HD-CT/PBSCT.

2. Patients and methods

58 relapsed patients were identified from a group of 286 consecutive patients with IGCCCG 'poor prognosis' GCT who had been treated between 3/93 and 3/01 with first-line HD-CT/PBSCT within two prospective German multicentre trials [6,9]. All patients who had relapsed until September 2001 were included in the analysis. Eligibility criteria for both HD-CT trials were identical and consisted of the following: 'advanced disease' according to the Indiana classification or, following the introduction of the IGCCCG classification in 1997, 'poor prognosis' non-seminomatous GCT, any primary site, normal kidney function unless impairment was tumour related and no prior chemotherapy. 221 patients had been treated with sequential high-dose VIP chemotherapy followed by PBSCT within the first German multicentre trial between January 1993 and November 1997. Treatment for these patients consisted of one cycle of standard-dose VIP chemotherapy (cisplatin 20 mg/m^2, etoposide 75 mg/m^2, ifosfamide 1200 mg/m^2 daily for 5 days) followed by 3–4 cycles of high-dose VIP chemotherapy with PBSCT. The dosages of the high-dose regimen were escalated inter-individually over eight dose levels and all patients treated from levels 3 to 8 requiring PBSC support were included. In contrast to the high-dose regimens used for the relapsed patients, the first-line regimen used in this study contained cisplatin as the most active agent in the treatment of GCT. We initially chose a cisplatin dose of 150 mg/m^2 per cycle based on data suggesting a benefit from cisplatin dose intensification [11,12]. However, during the time that our study was conducted, a randomised trial in patients with advanced disease demonstrated that doubling the dose of cisplatin did not lead to an improved outcome compared with a standard cisplatin-dose regimen [13]. Therefore, after an initial dose escalation up to 150 mg/m^2 per cycle, the cisplatin dose was reduced to the standard-dose of 100 mg/m^2 per cycle at dose level 6 and only etoposide and ifosfamide were further dose-escalated. The established standard-5-day chemotherapy cycles were used as a backbone for the escalation of the treatment doses.

The lowest dose level consisted of 30 mg/m^2 cisplatin, 200 mg/m^2 etoposide and 1600 mg/m^2 ifosfamide, each given for 5 days per cycle and the highest dose-level consisted of 20 mg/m^2 cisplatin, 300 mg/m^2 etoposide and 2400 mg/m^2 ifosfamide daily for 5 consecutive days every 3 weeks for a total of 3 HD cycles [6]. This regimen (dose level 6) serves as the high-dose chemotherapy arm of the ongoing randomised European Organization for Research and Treatment of Cancer (EORTC) trial 30974. 63 patients had received one cycle of standard-dose VIP chemotherapy as outlined above followed by three cycles of high-dose paclitaxel/VIP chemotherapy plus PBSC support within the subsequent prospective German multicentre phase I/II trial between January 1998 and March 2001 [9]. High-dose paclitaxel/VIP consisted of etoposide 300 mg/m^2, cisplatin 20 mg/m^2 and ifosfamide 2 g/m^2 daily for 5 consecutive days plus paclitaxel at a dose of 135–225 mg/m^2 (three dose levels) given over 3 h once every 3 weeks. All patients were scheduled to receive PBSC support ($>2\times10^6$ CD34+ cells/kg body weight retransfused per HD-CT cycle) and granulocyte-colony stimulating factor (G-CSF 5 μg/kg subcutaneously (s.c.) after HD-CT according to the treatment protocol.

The study protocols were approved by the Tuebingen University Ethics Committee and by the local Ethics Committees from the other involved sites.

The objectives of the present analysis included the description of treatment strategies and the identification of therapy- or patient-related factors that could predict

for response and survival in a cohort of patients with metastatic GCT failing first-line HD-CT/PBSCT. Patient variables and treatment characteristics were recorded for the analysis. There was no general recommendation for a specific salvage strategy in these patients. Feasibility of the various salvage regimens used was investigated. Response to salvage treatment was defined according to World Health Organization (WHO) criteria [14]. In addition, reduction of the size of a tumour lesion and normalisation of previously elevated tumour markers was considered a partial remission with tumour marker normalisation (PR−), whereas a reduction $\geqslant 50\%$ in the sum of the perpendicular diameters of measurable disease plus a tumour marker decrease for at least 1 month, but without complete normalisation, was considered a marker-positive partial remission (PR+). Serum tumour markers were determined every 2–4 weeks, depending on the salvage regimen and clinical indications. Evaluation of measurable disease by radiographical means was performed every 4–8 weeks depending on the treatment regimen chosen.

2.1. Statistical analysis

Data analysis was performed in cooperation with the Institute for Medical Information Processing at the University of Tuebingen. An explorative univariate analysis was performed in order to identify significant factors for response and survival. Correlations between preceding variables, response to salvage chemotherapy and survival were calculated by using the Fisher's Exact/Chi-square Tests and LogRank Test, respectively. The level of significance was set to 0.05. Progression-free survival after first-line HD-CT was calculated from the start of treatment until the date of relapse. The relapse-free interval between first-line therapy and relapse was calculated from the end of the first-line therapy until the date of relapse. The duration of follow-up, progression-free and disease-specific overall survival after relapse were calculated from the beginning of treatment for relapse to the date of last follow-up evaluation or the date of death. Survival curves were estimated by the method of Kaplan–Meier [15]. All tests were performed using SAS software (SAS Institute, Cary, NC, USA, version 6.11).

The following factors were included in the univariate analysis: response to first-line sequential HD-CT/PBSCT (CR/PR− versus PR+/NC/PD), location of primary tumour (gonadal/retroperitoneal versus mediastinal), number of metastatic sites at relapse ($\leqslant 1$ versus >1), secondary complete resection of residual masses after salvage therapy (for survival analysis only), presence of visceral metastases (yes/no), presence of central nervous system (CNS) metastases (yes/no) and/or pulmonary metastases (yes/no) (all at the time of relapse), type of salvage treatment (secondary HD-CT/PBSCT versus cisplatin-based standard-dose salvage therapy versus non-cisplatin-based chemotherapy or resection/radiation only), response to salvage therapy (for survival analysis only), interval between last HD-CT/PBSCT and the first salvage therapy (linear analysis from 1 month up to >12 months).

Multivariate analysis using the Cox Proportional Hazard Model was planned if the resulting subgroups contained >10 patients in order to allow a stable statistical model.

3. Results

3.1. Patient population

A total of 58 (20%) patients had relapsed in our patient population of 286 consecutive patients treated with first-line HD-CT/PBSCT within two successive prospective HD-CT trials by September 2001. Median progression-free survival following first-line HD-CT was 9 months (0–62 months). All 58 patients were included in the analysis. Patient characteristics are listed in Table 1. Primary tumour location was gonadal in 60%, mediastinum in 26%, and retroperitoneal in 14% of the patients. Treatment for relapse consisted of a second HD-CT plus autologous stem cell support in 14 (24%) patients, standard-dose cisplatin-based therapy in 19 (33%) and non-cisplatin-based chemotherapy in 16 (28%) patients. Non-cisplatin regimens, most of them administered within phase II studies, included single agent treatment with gemcitabine ($n=3$), paclitaxel ($n=2$), oxaliplatin ($n=4$), irinotecan ($n=1$) or oral etoposide ($n=2$), as well as the combination of gemcitabine/oxaliplatin ($n=2$) and bleomycin/vinblastine ($n=2$). 7 (12%) patients were treated with resection and/or radiation only and 2 (3%) patients were not treated due to their very poor performance status. The median relapse-free intervals following first-line HD-CT were 6.5 months (range: 0–59 months) for patients subsequently receiving salvage HD-CT, 6 months (range: 0–12 months) for patients being treated with standard-dose cisplatin-based chemotherapy and 5 months (0–8 months) for patients with non-cisplatin-based salvage therapy (these were not statistically different).

3.2. Response

55 patients are assessable for analysis of response to salvage treatment. One patient, who had received one cycle of single agent gemcitabine as salvage chemotherapy, was not assessable because he committed suicide prior to the response evaluation. 2 patients did not receive antitumour treatment due to rapid disease progression and subsequent worsening of their performance status.

Table 1
Characteristics of 58 patients relapsing after HD-CT/PBSCT as first-line treatment for 'Indiana advanced' or IGCCCG 'poor prognosis' metastatic germ cell cancer

Characteristics	Number of patients
Median age (years)	31 (17–55)
Location of primary tumour	
Gonadal	35 (60%)
Retroperitoneal	8 (14%)
Mediastinal	15 (26%)
First-line treatment:	
HD-VIP	42 (72%)
HD-Tax/VIP	16 (28%)
Response to first-line HD-CT:	
CR/PR-	34 (59%)
PR+	20 (34%)
NC/PD	4 (7%)
Relapse-free interval[a] between first-line CT and salvage therapy:	Median 6 months (0–59 months)
0–6 months	42 (72%)
7–12 months	13 (22%)
13–24 months	1 (2%)
>24 months	2 (3%)
Location of metastases at relapse[b]	
Lungs	17 (13%)
Visceral	23 (42%)
CNS	13 (57%)
Abdominal mass	7 (30%)
Liver	6 (26%)
Bone	4 (17%)
Type of salvage treatment:	
HD-CT	14 (24%)
Cisplatin-based standard CT	19 (33%)
Non-cisplatin-based CT	16 (28%)
Resection/radiation only	7 (12%)
No treatment	2 (3%)
Response to salvage therapy: ($n=55$[c])	
CR/PR−	21 (38%)
PR+	1 (2%)
NC/PD	32 (58%)
Therapy-related death	1 (2%)
Surgery after salvage treatment:	
Yes	24 (41%)
No	34 (59%)
Current status:	
Alive	18 (31%)
NED	10
CR	1
PR-	3
Alive with disease	4
Dead of disease	38 (66%)
Death other cause (suicide; secondary leukaemia)	2 (3%)
Median follow-up[d]	10 months (2–92 months)
2-year overall survival (all patients)[d]	32% (95% CI: 19–45%)

CT, chemotherapy; HD-CT, HD-CT plus autologous stem cell support; HD-VIP, etopside/ifosfamide/cisplatin; HD-Tax-VIP: paclitaxel/etopside/ifosfamide/cisplatin; CNS, central nervous system; CR/PR−/PR+, see methods for definitions; Nc, no change; PD, progressive disease; NED, no evidence of disease; CI, Confidence Interval.

[a] Calculated from the end of first-line treatment until the date of relapse.

[b] Based on 55 patients, 3 patients with no data on location of metastases.

[c] One patient committed suicide before response evaluation; 2 patients never received salvage treatment.

[d] Calculated from the time of relapse.

21 of 55 (38%) patients responded favourably to salvage therapy, with 9 patients achieving a complete and 12 patients a marker-negative partial remission. In these 21 patients, eight (38%) favourable responses were achieved after salvage HD-CT/PBSCT, six (29%) after standard-dose cisplatin- (+ other agents such as ifosfamide, paclitaxel, vinblastine) based chemotherapy and three (14%) after non-cisplatin-based chemotherapy. 2 of the latter patients responded to oral etoposide and the other patient to a combination of gemcitabine and oxaliplatin. 4 (19%) patients were in remission after surgery/radiation only.

Of all the variables examined, a statistical correlation on univariate analysis was found only with the use of salvage HD-CT/PBSCT. 8 of 14 (57%) patients receiving salvage HD-CT/PBSCT responded favourably, whereas only 9/35 (26%) patients with standard-dose cisplatin-based or non-cisplatin-based salvage chemotherapy achieved a complete or marker-negative remission.

3.3. Survival

At the time of this analysis, 38 (66%) patients had died of their disease, 18 (31%) patients are alive and 2 (3%) patients have died of cancer causes reasons after an overall median follow-up of 10 months (2–92 months) from the date of relapse. 30/38 (79%) deaths occurred within the first year after the initiation of salvage therapy. Patients responding to salvage treatment had a highly significant survival benefit with a projected 2-year disease-specific survival of 31% versus 7% for non-responding patients ($P=0.014$). Median survival since the diagnosis of relapse was 6 months (1–34 months) for patients who have died of their disease, whereas patients alive had a median survival of 27 months (2–92 months).

Of the 18 patients alive, 4 patients are alive with disease and 14 patients are in remission (1× CR, 3× PR−, and 10× NED). 6 of these 18 patients had received HD-CT/PBSCT, 5 cisplatin-based standard dose chemotherapy, 4 non-cisplatin-based chemotherapy and 3 patients resection/radiation only. 11 of these 18 patients underwent surgical resection of their tumour masses either prior or subsequent to the salvage chemotherapy (Table 2).

Of the 14 patients alive without disease, 11 had received salvage chemotherapy. Four (4/14; 29%) had been treated with salvage HD-CT/PBSCT, 5 (5/14; 36%) with cisplatin-based standard-dose and 2 (2/14; 14%) patients with non-cisplatin-based chemotherapy. 8 of these 11 patients underwent surgical resection of their tumour masses at some point during salvage treatment (1 patient prior to and 7 patients after salvage therapy). 3 patients received resection ($n=2$)/radiation ($n=1$) as the only salvage treatment and all 3 are currently alive with-

Table 2
Characteristics of patients alive (including 2 patients with GCT-unrelated deaths) ($n=20$)

Patient number	Primary tumour localisation	First-line therapy	Response to first-line HD-CT	Progression-free interval from first-line HD-CT to relapse (months)	Sites of relapse	First salvage regimen	Further salvage treatment	Duration of follow-up since relapse	Current status
1	Mediastinal	HD-VIP	CR	6	Liver, abdominal lymph nodes	Surgery (mature teratoma/ vital carcinoma)	–	36	NED
2	Gonadal	HD-VIP	CR	8	CNS, marker increase	Surgery followed by PEB ×2, HD-CE, RTx-CNS	–	71	NED
3	Gonadal	HD-Tax/VIP	PR–	1	Marker increase, CNS	Gemcitabine/oxaliplatin, surgery (vital carcinoma), RTX-CNS		4	NED
4	Gonadal	HD-VIP	PR–	3	Bone (hip)	RTx	–	80	PR–
5	Mediastinal	HD-VIP	PR–	3	Lungs, marker increase	TIP ×1, surgery (necrosis)	–	50	NED
6	Mediastinal	HD-VIP	PR–	15	Mediastinum	Surgery (sarcoma = non-germ cell cancer malignancy)	–	24	NED
7	Gonadal	HD-VIP	PR+	3	Lungs, CNS, marker increase	ECBC ×4, RTx-CNS	–	92	PR–
8	Gonadal	HD-VIP	PR–	4	Abdominal lymph nodes, lungs	HD-CT (VIP/CEC), surgery (vital carcinoma)	–	60	NED
9	Gonadal	HD-Tax/VIP	PR+	2	Lungs, liver, kidney, marker increase	PE×3, oral etoposide	Temozolamide, surgery (necrosis)	24	NED
10	Gonadal	HD-Tax/VIP	PR–	3	Lungs, marker increase	Oral etoposide		12	PR–
11	Gonadal	HD-Tax/VIP	PR+	1	CNS, lungs, marker increase	PVB, RTx-CNS, surgery (necrosis)		20	NED
12	Retroperitoneal	HD-Tax/VIP	PR–	1	Marker increase only	HD-CT (TIP/TEC), surgery (necrosis)		29	NED
13	Gonadal	HD-VIP	CR	39	Abdominal lymph nodes, marker increase	HD-CT (TIP/TEC)	–	20	CR
14	Gonadal	HD-Tax/VIP	PR–	2	CNS, liver	PVB×3, RT×,-CNS, surgery (necrosis)		21	NED
15	Mediastinal	HD-Tax/VIP	CR	4	Marker increase, mediastinum	Irinotecan	Gemcitabine/oxaliplatin, temozolamide, radiation therapy	10	AWD
16	Gonadal	HD-Tax/VIP	PR+	1	Lungs	Gemcitabine/Oxaliplatin		4	AWD
17	Gonadal	HD-VIP	PD	2	Abdominal lymph nodes, lungs	POMB-ACE	TIP	48	AWD
18	Gonadal	HD-VIP	CR	5	Abdominal lymph nodes, marker increase	HD-CT (T-ICE), Surgery (necrosis)	RTx-CNS, surgery (vital carcinoma)	15	AWD
19	Gonadal	HD-VIP	PR+	3	Marker only	HD-CT (TIP/TEC), Surgery (necrosis)	–	41	Death other cause (secondary leukaemia)
20	Gonadal	HD-VIP	PR–	2	Abdomen, mediastinum, lungs	Gemcitabine	–	5	Death other cause (suicide)

CR, complete remission; PR, marker-negative partial remission; PR, marker-positive partial remission; AWD, alive with disease;
TIP, paclitaxel, ifosfamide, cisplatin; TEC, thiotepa, etoposide, carboplatin; RTx, radiation therapy; PVB, cisplatin, vinblastine, bleomycin; VIP, etoposide, ifosfamide, cisplatin;
CEC, carboplatin, etoposide, cyclophosphamide; ECBC, etoposide, cisplatin, bleomycin, cyclophosphamide; POMB-ACE, cisplatin, vincristine, methotrexate, bleomycin, etoposide, actinomycin D, cyclophosphamide; T-ICE, paclitaxel, carboplatin, etoposide, ifosfamide.

out active disease. Of the 2 patients who died of GCT unrelated causes, 1 committed suicide during gemcitabine therapy and the other patient died of a secondary leukaemia without evidence of GCT following salvage HD-CT/PBSCT plus secondary resection.

Of the different variables evaluated by univariate analysis, only the use of HD-CT/PBSCT, the achievement of complete secondary surgical resection and response to salvage therapy attained statistical significance (Table 3). No other correlations were found, in particular the interval between first-line HD-CT/PBSCT and the initiation of salvage treatment was not predictive for the outcome of these patients.

No multivariate analysis was carried out, since the patient numbers of the resulting subgroups were too small (<10 patients) which would have led to a low stability of the statistical model and no reliable results could therefore be expected from the multivariate analysis.

Table 3
Prognostic variables for overall survival after salvage treatment

Factor	Number of patients in the cohort analysed	2-year survival rates (%)	*P* value
Primary tumour site			
gonadal/retroperitoneal	43	35	0.22
mediastinal	15	23	
Response to first-line therapy			
CR/PR−	37	36	0.55
PR+/NC/PD	21	26	
Presence of visceral metastases[a]			
Yes	23	21	0.25
No	32	39	
Presence of pulmonary metastases[a]			
Yes	17	27	0.97
No	38	33	
Presence of CNS metastases[a]			
Yes	14	31	0.68
No	41	32	
Number of metastatic sites[a]			
⩽1	30	40	0.15
>1	25	20	
Type of salvage treatment			
HD-CTX	14	48	**0.03**
Cisplatin-based standard-dose regimen	19	29	
Non-cisplatin-based chemotherapy	16	10	
Resection/radiation only	7	42	
Response to salvage therapy ($n=55$[b]):			
CR/PR−	21	31	**0.014**
PR+/NC/PD/toxic death	34	7	
Complete secondary surgery			
Yes	24	49	**0.015**
No	34	19	
Interval between first-line treatment and salvage therapy (median)			
⩽6 months	33	36	0.7
>6 months	25	36	

[a] Data of 3 patients missing.
[b] 1 patient committed suicide before response evaluation; 2 patients never received salvage treatment.

4. Discussion

There is little data available in the literature regarding the therapeutic strategies used and the outcome of metastatic GCT patients who have relapsed after first-line HD-CT/PBSCT. However, this issue is of increasing importance since first-line HD-CT/PBSCT is investigated in the US and in Europe in 'poor and intermediate prognosis' patients. Two randomised trials have currently enrolled a large number of patients. The EORTC trial 30974 uses the same HD-VIP regimen which was applied to 221 patients analysed in the present study. Based on the data available from phase II studies, approximately 20–30% of these patients will be potential candidates for salvage treatment after failure of first-line HD-CT/PBSCT. Since all of these patients have received very intensive and myelosuppressive first-line therapy, it has not yet been systematically investigated whether these patients can tolerate standard- or high-dose salvage therapy with a second PBSC transplant and also whether they will benefit from such salvage treatment.

In our investigation, almost all patients relapsing after first-line HD-CT/PBSCT received salvage therapy, with approximately half of them undergoing curatively intended combination chemotherapy; either a second HD-CT/PBSCT or standard-dose cisplatin-based chemotherapy, ± resection of residual masses. The choice of salvage treatment was made by the treating physician. Thus, the retrospective nature of our analysis makes it impossible to define the indications for the choice of a specific treatment option for each patient. It is likely that a cisplatin-based salvage chemotherapy was chosen if the patient's performance status was good and organ functions were well preserved. In almost a quarter of patients, a second HD-CT/PBSCT was performed. The choice of a second high-dose chemotherapy does not only require a relatively good performance status and the availability of autologous blood stem cells, either collected following one salvage cisplatin-based standard-dose chemotherapy cycle or left over from first-line therapy, but also needs an experienced treating physician. Thus, patient selection as a biasing factor has to be considered when interpreting the results of our study. Interestingly, response to first-line therapy and the relapse-free interval after first-line HD-CT — both representing cisplatin-sensitivity—, do not appear to have influenced the specific treatment option used since this interval was only 5–6 months for all of the patient subgroups.

Overall, this patient population had very poor prognostic factors, with almost a fourth of patients having a mediastinal primary tumour location and almost 50% having visceral metastases at the diagnosis of relapse. In addition, the sites of relapse included the CNS in almost 25% of patients. Despite these poor prognostic features, we observed a 2-year disease-specific survival rate of 32% after salvage treatment. As expected, patients responding to salvage therapy had a significant survival advantage over non-responding patients. On univariate analysis, the response to first-line chemotherapy or the number of metastatic sites at relapse or the location of the primary tumour, all of which are known prognostic factors for response to salvage HD-CT after failure from standard-dose first-line chemotherapy, were not significant prognostic factors for the outcome of salvage therapy in our study [16]. Tumour marker values before salvage treatment were not included in our analysis due to the lack of sufficient data. In contrast to patients receiving third- or fourth-line treatment, the length of the progression-free interval after first-line HD-CT/PBSCT also had no impact on survival or the response rate [17,18].

The achievement of a complete surgical resection of residual masses was associated with a significantly improved survival rate in our patient cohort. 10 of 14 patients currently alive without activity underwent complete surgical resection of their tumour masses demonstrating the importance of surgery as a component of the treatment in patients failing first-line high-dose chemotherapy. Previous studies have already demonstrated that long-term survival may be achieved in approximately 10–20% of relapsed or cisplatin-refractory patients with surgically resectable, localised disease [19,20]. Porcu and colleagues investigated the outcome of 101 patients relapsing from salvage high-dose chemotherapy. Only 5 patients were long-term survivors and all of these 5 patients had undergone complete resection of their tumour masses [18]. Fléchon and colleagues studied 32 patients, who had failed either first-line ($n=11$) or salvage high-dose chemotherapy ($n=21$). Similar to the results obtained by Porcu and colleagues, the most effective treatment was the resection of all residual masses [21]. Thus, secondary surgery appears to be an important element in the treatment of patients relapsing from high-dose chemotherapy and should therefore also be considered in patients with relapse after first-line HD-CT/PBSCT.

The use of a second HD-CT/PBSCT was the only significant variable correlated with both response to salvage therapy and survival. Patients receiving salvage HD-CT ± secondary surgery achieved a 2-year disease-specific survival rate of 48% (95% CI: 34–62%), whereas patients treated with cisplatin-based standard-dose regimens ± secondary surgery reached a 2-year disease-specific survival of only 29% (95% CI: 18–40%). These survival rates are very similar to the results achieved with salvage HD-CT or standard-dose cisplatin-based salvage therapy in patients failing first-line standard dose therapy. Of these patients, approximately 20–30% can be successfully salvaged with a second-line standard-dose cisplatin-based regimen and up to 50% with salvage HD-CT/PBSCT depending on the clinical characteristics of the patient [10,16,22–28].

The use of a second high-dose chemotherapy as a salvage therapy following relapse from first-line high-dose chemotherapy appears debatable. However, a significantly higher number of objective responses were observed following a second high-dose chemotherapy than following standard-dose chemotherapy. These patients are better candidates for subsequent surgical resection of residual tumours and may therefore do better than patients not responding to salvage chemotherapy. The chance for an objective response and, subsequently, for a better complete respectability of residual tumours seems to justify the use of a second high-dose or aggressive chemotherapy in selected patients. Thus, the results achieved in our study provide a strong rationale for the use of aggressive salvage treatment including the resection of all tumour masses in patients failing first-line HD-CT/PBSCT, if clinically feasible.

Similar to patients receiving non-cisplatin-based treatment following relapse from salvage high-dose chemotherapy patients treated without cisplatin in our study had a very poor prognosis [17,18]. Only 2 of these 16 patients have survived without evidence of active disease, to date both with a follow-up duration of less than 1 year indicating that non-platinum-based treatment is largely palliative and long-term survival is very rare. Radiation therapy appears to be a valuable therapeutic option in patients with CNS metastases or in patients with bone metastases.

Several limitations of the current study have to be considered. Some of the defined subgroups contained only a small number of patients, which may result in misleading interpretations of the data. In addition, the analysis considered only a limited number of clinical factors and it may be important to evaluate other factors in the future, such as histological subtypes, serum or molecular markers. However, the study was designed as an explorative retrospective investigation and therefore, provides only a small insight into the outcome of possible therapeutic options and factors correlating with survival in this patient population. In addition, the results are only based on an univariate analysis. A multivariate analysis was not performed since the patient numbers would not have allowed statistically reliable conclusions. Large, prospective studies are necessary in order to fully answer the questions regarding the optimal type of salvage treatment and prognostic factors in this patient population. However, assuming a relapse

rate of 30%, even the ongoing randomised trials will not provide significantly larger patient cohorts for a more extensive analysis than that given in our study.

In conclusion, despite the known limitations of a retrospective study, it appears that approximately 1/4 of patients relapsing after first-line sequential HD-CT/PBSCT may be successfully salvaged. Successful salvage treatment seems to be most likely achieved with the use of a second HD-CT/PBSCT in order to attain a remission and, most importantly, in patients in whom a subsequent complete secondary resection of residual masses is possible.

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