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Annals of Oncology 28: 1910–1916, 2017
doi:10.1093/annonc/mdx259
Published online 16 May 2017

ORIGINAL ARTICLE

Salvage high-dose chemotherapy in female patients with relapsed/refractory germ-cell tumors: a retrospective analysis of the European Group for Blood and Marrow Transplantation (EBMT)

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Note: These data have been presented in part during a poster session at the 2016 American Society of Clinical Oncology Annual Meeting (Abstract #5558).

Background: High-dose chemotherapy (HDC) with hematopoietic progenitor cell transplantation is a standard option for relapsed/refractory testicular germ-cell tumor (GCT), but only few data have been reported in female patients with GCT. We conducted a retrospective analysis of female patients with GCT treated with HDC and registered with the European Society for Blood and Marrow Transplantation.

Patients and methods: Between 1985 and 2013, 60 registered female patients with GCT, median age 27 years (range 15–48), were treated with salvage HDC. Forty patients (67%) had primary ovarian GCT, 8 (13%) mediastinal, 7 (12%) retroperitoneal and 5 (8%) other primary sites/unknown. Twenty-two patients (37%) received HDC as second-line therapy, 29 (48%) as third-line, and 9 (15%) as fourth- to sixth-line. Nine of 60 patients (15%) received HDC as late-intensification with no evidence of metastasis before HDC. The conditioning HDC regimens comprised carboplatin in 51 of 60 cases (85%), and consisted of a single HDC cycle in 31 cases (52%), a multi-cycle HDC regimen in 29 (48%).

Results: Nine cases who underwent late intensification HDC were not evaluable for response. Of the other 51 assessable patients, 17 (33%) achieved a complete response (CR), 8 (16%) a marker-negative partial remission (PRm−), 5 (10%) a marker-positive partial remission, 5 (10%) stable disease, and 13 (25%) progressive disease. There were 3 toxic deaths (6%). With an overall median follow-up of 14 months (range 1–219), 7 of 9 (78%) patients with late intensification and 18 of the 25 patients (72%) achieving a CR/PRm− following HDC were free of relapse/progression. In total, 25 of 60 patients (42%) were progression-free following HDC at a median follow-up of 87 months (range 3–219 months).

Conclusions: Salvage HDC based on carboplatin represents a therapeutic option for female patients with relapsed/refractory GCT.

Key words: high-dose chemotherapy, germ-cell tumors, female, relapsed, refractory, salvage therapy

Introduction

Malignant ovarian germ-cell tumors (GCT) are rare accounting for nearly 2%–3% of all ovarian tumors and occurring with an age-adjusted incidence rate of 0.3 per 100 000 adolescent and young women with a median age of nearly 20–25 years [1]. Most female patients with GCT achieve sustained remissions following first-line cisplatin-based chemotherapeutic regimens, but a small percentage progress and is commonly treated with ifosfamide and cisplatin-based chemotherapeutic regimens mirroring regimens used for men with relapsed GCT [2, 3]. High-dose chemotherapy (HDC) with peripheral blood progenitor cell (PBPC) support is an accepted and feasible option for salvage treatment in male patients with relapsed GCT taking into consideration large series of retrospective data [4, 5]. HDC is considered an option together with other standard-dose regimens as second-line therapy and represents the treatment with the highest chance of cure as third-line or subsequent therapy for these patients [5, 6]. Moreover, in children with relapsed GCT HDC showed impressive results and is considered a possible option as salvage treatment [7]. A few small series have reported salvage HDC in female patients with relapsed/refractory GCTs [8, 9].

We conducted a retrospective analysis of female patients with GCT treated with salvage HDC registered with the European Society for Blood and Marrow Transplantation (EBMT).

Methods

Data collection

From 1985 to 2013, a total of 114 patients aged ≥15 years with a diagnosis of female GCT were registered with the EBMT. Female GCT may include dysgerminomas and non-dysgerminomas. Non-dysgerminomas were classified as embryonal carcinoma, choriocarcinoma, yolk sac tumor, immature teratoma, and mixed GCT, according to the World Health Organization classification. Patients with a non-ovarian primary tumor site (extragonadal GCT) were included, whereas patients with gestational trophoblastic neoplasms (e.g. gestational choriocarcinoma) were excluded from this report. The registration details of these patients were reviewed, and the reporting physicians were contacted and asked to provide further information on histology, tumor markers, initial treatment, standard chemotherapy, HDC regimens and toxicities, PBPC and/or autologous bone marrow transplantation (BMT) support, follow-up and data on possible secondary neoplasms. For data collection, a standardized questionnaire was sent to each center. Of 114 registered cases, 60 questionnaires were returned (redemption rate, 53%) from 25 centers in Europe.

Definitions

Tumor response was classified as follows. A complete remission (CR) was defined as a complete disappearance of all clinical, radiological and biochemical evidence of disease. A partial response (PR) was defined as a decrease in 50% or more of the sum of the products of perpendicular diameters of measurable disease, with a decrease of ≥90% of tumor markers, including normalization of tumor markers considered as a partial remission with tumor marker normalization (PRm–) and without complete normalization considered as a marker positive partial remission (PRm+). Stable disease (SD) was defined as a decrease <50% or an increase <25% in bidimensional tumor measurements or stable tumor marker levels. Progressive disease (PD) was defined as either residual lesions increasing in size or as occurrence of new lesions and/or elevation of tumor markers.

Statistical analysis

Descriptive statistics are presented as count and relative frequency for categorical data and the median and range for continuous data. Overall survival (OS) was defined as the time from HDC to death from any cause or last follow-up, and progression-free survival (PFS) was defined as the time from HDC to relapse or PD or death from any cause, whatever came first, or last to follow-up. Probabilities of OS and PFS were estimated using the Kaplan–Meier product limit method and were compared using the log-rank test. A P value of <0.05 was considered to be significant. Statistical analyses were carried out with SAS 9.4 software (SAS Institute, Cary, NC).

Results

Study population characteristics

Between 1985 and 2013, 60 registered female patients with GCT aged ≥15 years were treated with salvage HDC, median age was 27 years (range 15–48). Thirty-eight (63%) patients had primary ovarian GCT, 11 (18%) mediastinal, and 11 (18%) other extragonadal primary sites. Fifty-nine (98%) patients received at least one cisplatin-based chemotherapy before HDC, while one (2%) 15-year-old girl received carboplatin-based chemotherapy only before HDC. Details of the patient characteristics before HDC are listed in Table 1.

Salvage treatment

Between 1985 and 1990, 11 (18%) patients were treated with 15 courses of a HDC regimen, between 1991 and 2000 23 (38%) patients received 30 courses, and 2001 and 2013 26 (43%) patients 45 courses. Twenty-two patients (37%) received HDC as second-line therapy, 29 (48%) as third-line, and 9 (15%) as fourth- to sixth-line. Nine of 60 (15%) patients received HDC as late-intensification of a previous regimen without evidence of metastasis at the time of HDC. The planned conditioning HDC regimens consisted of a single cycle in 31 cases (52%) and a multi-cycle regimen in 29 (48%), consisting of 2 HDC cycles in 25 cases and 3 HDC cycles in 4. However, in 2 cases the second planned HDC cycle was not carried out due to toxic death after the first one, so totally 90 HDC cycles were administered. The most commonly used HDC regimens were based on high-doses of carboplatin and etoposide, with or without another high-dose chemotherapeutic agent and comprised carboplatin in 51 of 60 cases (85%) (Table 2). Before HDC, 37 (62%) patients received an induction and/or mobilizing regimen, more frequently VIP (cisplatin, etoposide and ifosfamide) ($n=15$, 41%), while 23 (28%) patients were treated with up-front HDC. In total, 61 courses in 37 patients were supported by PBPC reinfusion, 28 courses in 22 patients were supported by BM reinfusion, and 1 course was supported by both BM and PBPC reinfusion.

Response and survival

Nine cases who underwent late intensification HDC were not evaluable for response. Of other 51 patients treated with salvage

Table 1. Patient characteristics before high-dose chemotherapy

Characteristics	*n* (%)
Age, years	
Median (range)	27 (15–48)
Primary site	
Ovary	38 (63%)
Mediastinum	9 (15%)
Mediastinum and retroperitoneum	2 (3%)
Retroperitoneum	4 (7%)
Sigmoid colon	2 (3%)
Pineal/pituitary gland	1 (2%)
Other/unknown	4 (7%)
Histological type	
Yolk sac tumor	20 (33%)
Embryonal carcinoma	9 (15%)
Non-dysgerminoma—mixed form	9 (15%)
Non-gestational choriocarcinoma	7 (12%)
Dysgerminoma	3 (10%)
Other/unknown	12 (20%)
Metastatic sites before HDC	
Retroperitoneum	19 (32%)
Lung/pleura	19 (32%)
Liver	12 (20%)
Mediastinum/neck	11 (18%)
Peritoneum	5 (8%)
Other/unkonwn	12 (20%)
HDC line of therapy	
2nd line	22 (37%)
3rd line	29 (48%)
4th to 6th line	9 (15%)
HDC setting	
HDC at PD after a previous CT	51 (85%)
HDC as late intensification	9 (15%)
HDC regimens	
Carboplatin-based	51 (85%)
Other	9 (15%)
HDC n. courses	
Single cycle	31 (52%)
Multi-cycle	29 (48%)
Hematopoietic support	
Peripheral blood progenitor cells	37 (62%)
Bone marrow transplantation	22 (37%)
Both PBPC and BMT	1 (2%)

HDC, high-dose chemotherapy; CT, chemotherapy; PBPC, peripheral blood progenitor cells; BMT, bone marrow transplantation.

Table 2. Details of high-dose chemotherapy regimens

HDC regimen	*n* of patients (%)	*n* of HDC courses (%)
Carboplatin–etoposide–cyclophosphamide	21 (17%)	25 (17%)
Carboplatin–etoposide–ifosphamide	14 (33%)	24 (33%)
Carboplatin–etoposide[a]	13 (33%)	22 (33%)
Carboplatin–etoposide–thiotepa	3 (25%)	3 (25%)
Thiotepa–paclitaxel	3 (25%)	7 (25%)
Thiotepa–cyclophasphamide	2 (25%)	3 (25%)
Etoposide–ifosfamide–cisplatin	2 (25%)	3 (25%)
Etoposide–ifosfamide	1 (25%)	2 (25%)
Melphalan–etoposide	1 (25%)	1 (25%)

aIn a patient, in two courses of CE, vinblastine was given in addition.
HDC, high-dose chemotherapy.

HDC at PD from a previous line of therapy, 24 (47%) obtained an objective response, including 15 (29%) CR and 9 (18%) PRm−, 5 (10%) patients achieved PRm+, 5 (10%) SD, 13 (25%) PD, 1 (1%) case was considered not evaluable for response, whereas in 3 (6%) cases treatment-related deaths occurred. Of 9 patients with PRm− after HDC, 6 (67%) received the surgical resection of residual masses, in 4 cases without evidence of viable malignant cells in the histological specimen (pathological CR), and in the other 2 with presence of viable malignant cells (surgical CR). In one case with pathological CR, a post-surgical adjuvant retroperitoneal radiotherapy was given. Treatment-related death occurred in three patients treated with HDC supported by ABMT in 1988, 1989, and 1994, respectively; all these three cases had a cisplatin-refractory ovarian GCT, defined as PD as best response to previous cisplatin-based chemotherapy.

With a median follow-up time for all patients of 14 months (range 1–219 months), 7 of 9 (78%) patients who underwent late intensification and 18 of the 24 patients (72%) who achieved an objective response following HDC were alive free of relapse/progression. Overall, with at a median follow-up period for surviving cases of 84 months (range 3–219 months), 25 (42%) of 60 patients were continuously progression-free following HDC, including 7 treated with late intensification HDC, while 26 (44%) were alive following HDC, 13 (59%) of 22 treated as initial salvage setting and 13 (34%) of 38 at later stages. The median PFS time was 9 months (95% CI 4.3–not reached) and the median OS time was 27.6 months (95% CI 8.9–48.5). The 3-year OS rate for these patients was 43%. Figure 1 shows Kaplan–Meier estimates of PFS and OS for these patients.

The response rate and the clinical outcome of patients was different according to the gonadal or extragonadal GCT primary site (Table 3). The median PFS time was 19.2 months (95% CI 4.3–not reached) for patients with primary ovarian GCT, 11.8 months (95% CI 1.9–not reached) for extragonadal non-mediastinal primary GCT and 6.9 months (95% CI 1.0–20.9) for patients with mediastinal primary site ($P = 0.175$). The median OS time was 30.8 months (95% CI 9.1–not reached) for patients with primary ovarian GCT, 27.6 months (95% CI 4.5–not reached) for extragonadal non-mediastinal primary GCT and 7.4 months (95% CI 5.2–47.0) for patients with mediastinal primary site ($P = 0.100$). The 3-year OS rates for these three groups of patients were 47%, 31%, and 23%, respectively. There was not difference in the median PFS and OS among patients treated with single or multicycle HDC regimens (data not shown), however, several HDC regimens were used and for every HDC regimen one or more cycles were administered (Table 2).

In patients treated with HDC as second-line therapy, the median PFS and OS time was not reached, whereas in those treated

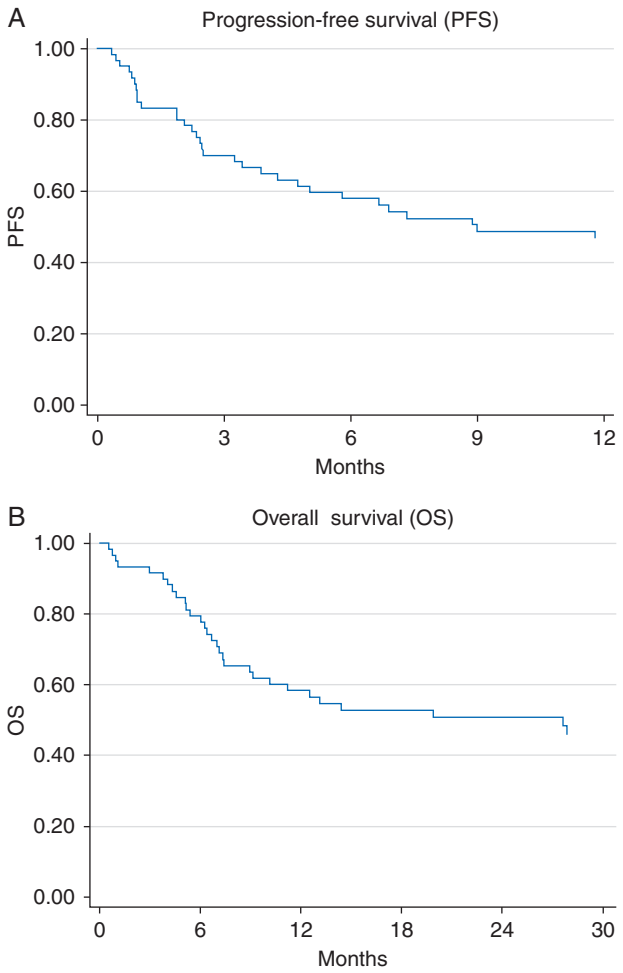

Figure 1. Kaplan–Meier estimates of progression-free survival (A) and overall survival (B).

as third or further line of therapy the median PFS time was 5.8 months (95% CI 2.15–11.8), $P = 0.031$, while the median OS time was 11.2 months (95% CI 7.0–27.9), $P = 0.035$. Figure 2 illustrates PFS and OS according to the primary site, and the number of previous line of therapies.

All three patients with dysgerminoma had primary ovarian GCT and with HDC achieved CR, PRm−, and SD, respectively, but none maintained a disease-free status and all three patients died within one year from HDC.

No cases of secondary leukemia or myelodysplasia were reported in these patients, but one case of breast cancer occurred in a woman aged <35 years in a disease-free status from GCT after HDC.

Discussion

Due to the rarity of the disease and the high curability in the primary setting, there are limited cases series on the salvage treatment of female patients with relapsed/refractory GCT. To our knowledge, the 60 female patients who received salvage HDC in our study represents the largest group yet reported in this setting. In the EBMT experience, salvage HDC appeared active in female GCT patients with 43% alive and progression-free at a median follow-up of 7 years in surviving patients, whereas long-term survival was reported in only 10% of patients treated with standard-dose salvage chemotherapy in the major retrospective series [3]. Yolk sac histology was the

prevalent histology in relapsed/progressing patients in our series as well as other major ones [8, 10]. Extragonadal GCT accounts for nearly 10% of all female GCT in adolescent and young women [11], but in our series focused on relapsed/progressing patients the extragonadal GCT accounted for the 37%, confirming the poor prognosis of this subset of patients. Toxic death occurred in 2 of 11 (18%) patients treated with HDC with BMT

Table 3. Response and outcome according to primary tumor site

	Primary site			
	Total (*n*=60) [*n* (%)]	**Gonadal** (*n*=38) [*n* (%)]	**Mediastinum** (*n*=11) [*n* (%)]	**Extra-gonadal non-mediastinal** (*n*=11) [*n* (%)]
Response				
Complete remission	15 (25%)	9 (24%)	2 (18%)	4 (36%)
Partial remission with negative marker	9 (15%)	5 (13%)	2 (18%)	2 (18%)
Partial remission with positive marker	5 (8%)	2 (5%)	2 (18%)	1 (9%)
Stable disease	5 (8%)	4 (11%)	0	1 (9%)
Progressive disease	13 (22%)	6 (16%)	4 (36%)	3 (27%)
Treatment-related death	3 (6%)	3 (8%)	0	0
Not evaluable	1 (2%)	0	1 (9%)	0
Late intensification	9 (15%)	9 (24%)	0	0
Outcome				
Alive continuously disease-free	25 (42%)	19 (50%)	2 (18%)	4 (36%)
Alive currently disease-free	0	0	0	0
Alive with disease	1 (2%)	0	0	1 (9%)
Dead of disease	31 (52%)	16 (42%)	9 (82%)	6 (55%)
Treatment-related death	3 (5%)	3 (8%)	0	0

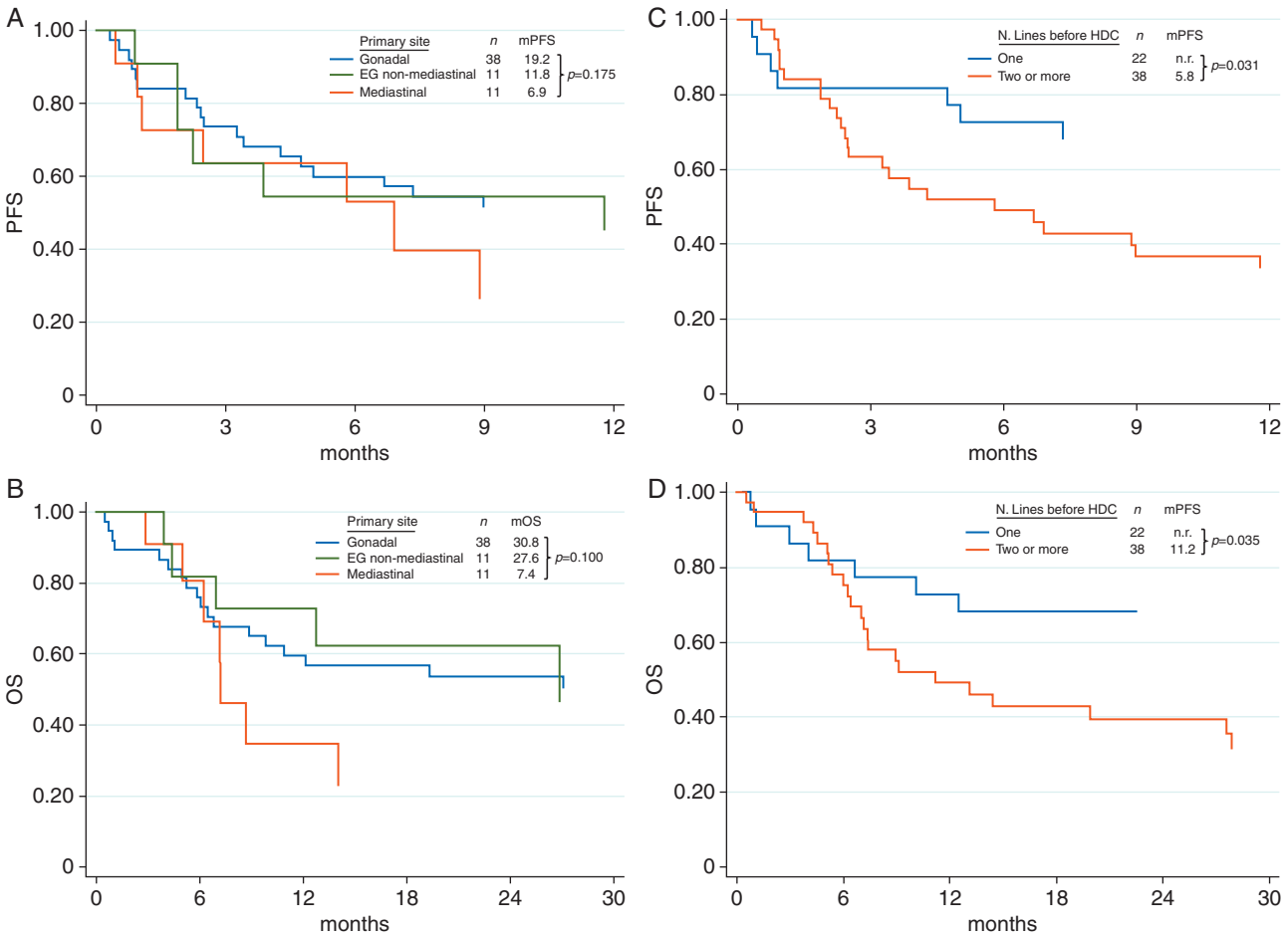

Figure 2. Kaplan–Meier estimates of progression-free survival and overall survival according to primary tumor site (A and B, respectively) or according to the number of previous therapeutic lines (C and D, respectively). EG, extragonadal; *n*, number; mPFS, median progression-free survival; mOS, median overall survival; n.r., not reached.

support without colony-stimulating factors between 1986 and 1990, and 1 of 23 (4%) treated with HDC and BM support between 1991 and 2000, whereas no cases of HDC-related death occurred in the 26 cases treated with HDC after 2001. The high treatment-related mortality (18%) that occurred in our patient series in the 1980s was similar to the mortality observed in other major series during the same period [12–15]. However, with improved patient selection and supportive care, the HDC-related mortality decreased to 4% in the 1990s and no cases in 2000s. One case of breast cancer occurred, whereas no patient developed myelodysplasia or secondary leukemia after receiving HDC.

Patients with mediastinal primary GCT had not statistically significantly different PFS and OS from those with other primary sites, however, a significant trend for poorer PFS and OS was apparent (Figure 2A and B). Furthermore, only 11 patients had a mediastinal primary GCT which likely contributed to the low statistical power in this tumor characteristic. Mediastinal primary site is recognized as a poor risk factor in male patients with nonseminomatous GCT not only at diagnosis [16, 17], but also before salvage chemotherapy where represents the poorest prognostic factor [18, 19]. Larger case series are needed to verify the potential impact of mediastinal primary site in the prognosis of female patients with GCT. Results with HDC in other extragonadal GCT patient populations, as first-line late intensification in male patients [17], and as salvage treatment in extragonadal GCT in children [7] confirmed the activity of HDC even in these extragonadal GCT patients, but the impact of HDC in mediastinal primary GCT remains controversial. We also evaluated patients treated with HDC as second-line therapy versus those treated as third or further line of therapy, the median PFS and OS were statistically significantly different confirming a better outcome for patients treated with HDC as first salvage option (Figure 2C and D). Different HDC regimens were administered with different number of cycles (Table 2), so an analysis of the impact on the clinical outcome of different regimens and/or the number of HDC cycles was not possible. However, in male patients with GCT modern HDC regimens are based on two or three cycles of high-dose carboplatin and etoposide, so these multicycle HDC regimens should be adopted for salvage treatment of female GCT [6, 20].

Limitations to this study are the retrospective nature, the limited number of cases in a large time period, the pathology was not centrally reviewed and misclassification of tumors could have occurred. However, our data provide evidence that patients with recurrent female GCT can achieve long-term disease-free survival and cure potential with salvage HDC, in particular as initial

salvage setting with 13 (59%) of 22 patients, but with long-term PFS status also in 13 (34%) of 38 in whom HDC was attempted as third-line or later treatment. Recently reported data from Indiana University have shown long-term PFS in 3 (60%) of 5 female GCT patients treated with HDC as first salvage compared with only 1 (13%) of 8 who received HDC with later stages [8]. Another recent experience from Memorial Sloan Kettering has shown similar results with long-term PFS achieved in 4 (67%) of 6 female GCT patients who received HDC as initial salvage, and in 2 (29%) of 7 patients as later salvage setting [9].

For female GCT, more effective treatments for poor prognosis and relapsed advanced disease are needed. Randomized trials evaluating new regimens in this setting might be conducted only as a portion of male GCT studies with international collaboration [21].

In conclusion, this study suggests that salvage HDC represents a valid therapeutic option for female patients with relapsed/refractory GCT. Further collaborative retrospective studies are needed to provide adequate data to try to define which relapsed patients benefit most from salvage HDC. Female patients with GCT should be included in phase II and III studies with HDC in male patients with GCT to have the opportunity to provide prospective data in this rare group of patients.

Acknowledgements

We thank all investigators and collaborators involved in the study. Investigators at the following hospitals participated in the study (number of patients contributed to final analysis): S. Richard, F. Selle, Hopital Tenon, Paris, France ($n=11$); U. De Giorgi and G. Rosti, IRST IRCCS Meldola and Ravenna, Italy ($n=10$); E. Kanfer Imperial College, London, UK ($n=5$); J. H. Bourrhis Institute Gustave-Roussy, Villejuif, France ($n=4$), E. Nicolas-Virelizier, Centre Leon Berard, Lyon France ($n=3$); K. Vettenranta, University of Helsinki, Helsinki, Finland ($n=3$); B. Lioure, Hôpital Civil, Strasbourg, France ($n=2$), S. Martin, Robert-Bosch-Krankenhaus, Stuttgart, Germany ($n=2$); P. Dreger, University of Heidelberg, Heidelberg, Germany ($n=2$); M. K. Schuler, University of Dresden, Dresden, Germany ($n=2$); K. Thomson, Department of Haematology, University College London Hospital London ($n=2$); M. Michieli, Centro di Riferimento Oncologico, C.R.O. IRCCS, Aviano, Italy ($n=1$); D. Bron, Institut Jules Bordet, Brussels, Belgium ($n=1$); W. Siegert, Charité Universitätsmedizin, Berlin, Germany ($n=1$); A. Ganser, Hannover Medical School, Hannover, Germany ($n=1$); T. Kozák, Charles University, Prague, Czech Republic ($n=1$); D. Laszlo, European Institute of Oncology, Milan, Italy ($n=1$); E. Jost, University Hospital, Aachen, Germany ($n=1$); H. Ayad Ahmed, King Hussein Cancer Centre, Amman, Jordan ($n=1$); A Spencer, Alfred Hospital, Melbourne, Australia ($n=1$); P. Ljungman, Karolinska University Hospital, Stackolm, Sweden ($n=1$); M. Hentrich, Klinikum Harlaching, Munich, Germany ($n=1$); C. Bokemeyer, Universitätsklinikum Hamburg-Eppendorf, Hamburg, Germany ($n=1$); B. Metzner, Klinikum Oldenburg, Oldenburg, Germany ($n=1$); D. Caillot, CHU, Dijon, France ($n=1$). We also thank all other hospitals participating in the EBMT Solid Tumours Working Party (STWP) network.

Funding

None declared.

Disclosure

The authors have declared no conflicts of interest.

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