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ORIGINAL RESEARCH

High-dose chemotherapy with autologous stem cell transplants in adult primary non-seminoma mediastinal germ-cell tumors. A report from the Cellular Therapy and Immunobiology working party of the EBMT

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Background: Primary mediastinal germ-cell tumors (PMGCTs) account for 1%-3% of all germ-cell tumors (GCTs). Non-seminoma have a poorer prognosis compared to their gonadal counterpart and, according to the International Germ Cell Cancer Collaborative Group, they are considered 'poor risk' disease. Medical treatment is the same, with overall survival (OS) being ∼40%, declining to 10%-15% at 3 years in case of lung and non-visceral metastases. Patients failing first-line chemotherapy have a dismal prognosis, with only 5%-10% of cases being cured in the salvage setting. High-dose chemotherapy (HDC) with autologous stem cell transplantation (ASCT) has been successfully used to treat patients with relapsed or refractory gonadal GCTs.

Patients and methods: This retrospective study aimed to investigate the value of HDC with ASCT in the whole population and define primary mediastinal non seminoma germ cell tumor (PMNSGCT) patient subgroups, who were registered in the European Society for Blood and Marrow Transplantation database from January 2000 to January 2018. Sixty-nine adult male patients with PMNSGCT were included. HDC consisted mainly of carboplatin/etoposide doublet, and most patients received HDC as part of a multiple sequential HDC program.

Results: OS was 43.3% at 2 years, and 34.7% at 5 and 10 years for the entire cohort. Analysis of outcomes showed that patients undergoing HDC as upfront therapy had a better progression-free survival (PFS) and OS compared to those treated in subsequent relapses (5-year PFS 51.8% versus 26.8% and 5-year OS 51.3% versus 25.9%). Better remission status before transplantation was predictive of the benefit of HDC. Three treatment-related deaths were recorded.

Conclusions: To our knowledge, this is the most extensive retrospective study of HDC in PMNSGCTs patients and the first to thoroughly investigate potential predictors of benefit from this treatment. HDC with ASCT may well represent a therapeutic option in patients with PMNSGCTs after the first relapse or even as a front-line program.

Key words: high-dose chemotherapy, stem cell transplantation, primary mediastinal germ-cell tumors

INTRODUCTION

Germ-cell tumors (GCTs) are a group of tumors usually arising in the gonads (testes or more rarely in the ovaries). They are highly sensitive to chemotherapy (CT) and, in the case of seminoma, to radiotherapy (RT).[1,2]

GCTs occur very rarely in sites outside the gonads, mainly in the retroperitoneum and anterior mediastinum while they are extremely unusual in the pineal gland or the sacrococcygeal area.[3]

Primary mediastinal germ-cell tumors (PMGCTs) account for 15% of adult mediastinal cancers,[4] constituting 1%-3% of all GCTs. According to the most accepted hypothesis,

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PMGCTs arise because germ cells stop their descent to the gonads despite the presence of otherwise normal testes, and remain in the anterior mediastinum where they eventually become malignant.[5]

The mean age at diagnosis is 25-35 years and, in contrast to testicular cancer, no increase in incidence in the following decades has been reported.[6]

The clinical course of PMGCTs should be differentiated into the main histologic groups, seminoma, and non-seminoma. Mediastinal seminomas have the same prognosis as gonadal tumors, while non-seminomas (primary mediastinal non seminoma germ cell tumor [PMNSGCTs]) yield a distinguished phenotype characterized by higher chemoresistance and shorter survival. According to the International Germ Cell Cancer Collaborative Group (IGCCCG),[2,7] it is considered by definition as a 'poor risk' disease, with only no more than 40%-50% of patients cured with first-line CT compared with >80% for testicular NSGCTs.[8]

The results of second-line therapy in testicular cancer are better than those achieved in other solid tumors, as a significant proportion of GCTs can still be cured. In contrast, the outcome for PMNSGCTs failing first-line CT is dismal, with only ∼5%-10% of patients being cured, irrespective of the regimen used.[1,9,10]

HDC with autologous stem cell transplantation (ASCT) has been successfully used to treat patients with relapsed or refractory GCTs.[11] Early trials of HDC were first introduced in the 1980s and it was suggested that this approach might favorably affect the course of chemosensitive malignancies.[12] Because of the extremely high chemosensitivity of GCT, HDC has been rapidly investigated in various settings. Currently, HDC is a therapeutic option for patients with disease refractory to platinum-based CT, with a second or further relapse, or as a second-line in high-risk patients, and not recommended as first-line therapy except in some European countries.[13,14]

This report, aimed to better characterize the role of HDC in PMNSGCTs, is a retrospective analysis of the large database of patients registered within the European Society for Blood and Marrow Transplantation (EBMT). The EBMT is a non-profit organization established in 1974 to allow scientists and physicians involved in stem cell transplantation to share their experiences and develop cooperative studies. The EBMT is divided into working parties; the Cellular Therapy and Immunobiology Working Party, which includes the solid tumor subcommittee, is dedicated to preclinical, translational, and clinical (comprehending retrospective) studies, including autologous and allogeneic SCT, and active and adoptive immunotherapy. EBMT centers, which are distributed in >60 countries, are required to send patient data, including demographic and clinical, to the central EBMT database on a yearly basis.

PATIENTS AND METHODS

Data collection

The EBMT database was interrogated to identify suitable patients for this study. The diagnosis of PMNSGCT was defined as a germ-cell neoplasm arising in the anterior mediastinum without demonstrable testicular abnormalities. Inclusion criteria were male patients, ≥18 years, receiving ASCT between 2000 and 2018. Patient selection, data extraction, quality control, and checks for consistency were made at the EBMT Office in Paris. A standardized questionnaire was sent to each center to provide additional information on the extent of the disease, histology, tumor markers, type of treatment, number of therapeutic lines, HDC drugs, source of hematopoietic stem cell, toxicities, and follow-up. Data from 69 patients with a diagnosis of PMNSGCT treated with HDC and ASCT between January 2000 and December 2018 were collected from 19 centers in nine European countries. Since the 1 January 2003, all transplantation centers have been required to obtain written informed consent before data registration with the EBMT, as per the Declaration of Helsinki of 1975. Data accuracy is assured by the individual transplant centers and by quality control measures such as regular internal and external audits.

Statistical analysis

Primary outcomes were OS defined as the time to death from any cause and progression-free survival (PFS) defined as survival with no evidence of relapse or progression. PFS and OS were measured from the date of the first ASCT. Probabilities of OS and PFS were calculated using the Kaplan—Meier method. Univariate analyses were done using the log-rank test. Median follow-up was calculated using the reverse Kaplan—Meier method. A Cox proportional hazards model was used for multivariate analyses by including patient age, status at transplant, and line of treatment (HDC upfront or as a subsequent line of therapy). Results were expressed as the hazard ratio (HR) with a 95% confidence interval (CI). All tests were two-sided with a type 1 error rate fixed at 0.05. Statistical analyses were carried out with SPSS 25.0 (IBM Corp., Armonk, NY) and R 4.2.3 [R Core Team (2023); R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria, https://www.R-project.org/].

Patient and treatment characteristics

Details of the 69 patients with PMNSGCTs during primary cisplatin-based CT, or relapsed thereafter, are listed in Table 1. The median age was 31 years (range 19-71 years). Forty-two patients (63.6%) had a metastatic disease, and 24 (36.4%) had a locally advanced disease; data were missing in three patients. Data on conventional CT before HDC were available in 23 patients (33.3%); among them, 16 patients (69.5%) received the TIP (taxol, cisplatin, and ifosphamide) regimen. Before HDC, 31 patients (45%) underwent surgery that achieved complete or partial tumor resection in 15 and 3 patients, respectively; data on the outcome of surgery were missing in 12 patients. Details on treatments before HDC are reported in Table 1.

Thirty-five patients (56.5%) were in complete or partial response at transplant, while 27 (43.5%) had stable or

Table 1. Patients characteristics

Characteristics	N = 69
Age (years)	
Median	31
Range	19-71
Disease extension, *n* (%)	
Metastatic disease	42 (63.6)
Locally advanced	24 (36.4)
Unknown	3
Prognosis risk[a], *n* (%)	
Poor	69 (100)
Time to relapse[b] (months)	
Median	4.5
Range	<1-24.7
Standard therapy before HDC, *n* (%)	
TIP	11 (47.8)
Gem-TIP	1 (4.3)
VIP	6 (26)
Other	5 (21.7)
Missing data	46
Status at transplant, *n* (%)	
CR	9 (14.5)
PR	26 (37.6)
SD	4 (6.5)
PD	23 (33.3)
Missing data, *n*	7

CR, complete response; Gem, Gemcitabine; HDC, high-dose chemotherapy; PD, progression disease; PR, partial response; SD, stable disease; TIP, taxol, ifosphamide, cisplatin; VIP, cisplatin, etoposide, ifosphamide.
[a]According to the IGCCCG (International Germ Cell Cancer Collaborative Group).
[b]Time from completion of first line to relapse after first-line treatment.

Table 2. Treatment characteristics and outcomes

Characteristics	N = 69
Mobilization regimen, *n* (%)	
Chemotherapy + G-CSF	63 (94)
G-CSF only	4 (6)
Missing	2
Preparative regimen, *n* (%)	
Carboplatin-etoposide	37 (53.6)
Taxane containing	11 (15.9)
ICE	8 (11.6)
VIP	7 (10.2)
Other	6 (8.7)
HDC, *n* (%)	
Upfront	24 (34.8)
First relapse	23 (33.3)
Second relapse	15 (21.7)
Third relapse	6 (8.7)
Fourth relapse	1 (1.4)
Number of transplant, *n* (%)	
One	3 (4.4)
Two	37 (53.6)
Three	29 (42)
Outcomes after HDC, *n* (%)	
Complete remission	21 (35.6)
Partial remission	15 (25.4)
Never responding	23 (39)
Missing	10
Surgery after HDC, *n* (%)	
Complete	17 (24.6)
Incomplete	3 (4.3)

G-CSF, granulocyte colony-stimulating factor; HDC, high-dose chemotherapy; ICE, carboplatin, etoposide, ifosphamide; VIP, cisplatin, etoposide, ifosphamide.

progressive disease at transplant; status at transplant was missing in 7 patients.

Sixty-three patients (94%) received CT as part of the mobilization regimen, while four patients (6%) received granulocyte colony-stimulating factor (G-CSF) only; data were missing in two patients. Twenty-four patients (34.8%) received HDC as upfront treatment, 23 patients (33.3%) as first-line therapy after relapse, and 22 (31.9%) as second or subsequent lines. Most patients (95.6%) received HDC as part of multiple sequential programs of HDC. The most commonly used HDC protocols were based on high doses of carboplatin and etoposide (53.6%).

Table 2 summarizes treatment characteristics and outcomes.

RESULTS

The median follow-up was 9.1 years. In the whole population, the PFS at 2, 5, and 10 years was 41.3%, 35.8%, and 35.8%, while the OS was 43.3%, 34.7%, and 34.7%, respectively (Figure 1). Because no difference in PFS and OS was observed beyond 5 years, patients alive at 5 years can be considered cured.

In univariate analysis, patients undergoing HDC as upfront therapy (Figure 2A) had a better PFS and OS compared to those treated in subsequent relapses (5-year PFS 51.8% versus 26.8% and 5-year OS 51.3% versus 25.9%). Status at HDC in complete response (CR) or partial response (PR) (Figure 2B) was associated with better PFS and OS compared to patients with stable disease or progressive disease (PD) (5-year PFS 50% versus 25% and 5-year OS 48% versus 22%). In multivariate analysis, adjusted for patient age, one or more lines versus upfront therapy was associated with a lower PFS (HR = 2.61, 95% CI 1.3-6.63, $P = 0.043$) and trends for a lower OS (HR = 2.28, 95% CI 0.97-5.39, $P = 0.059$). Forty patients (58%) had a relapse of their disease with a median time to relapse of 4.8 months.

Twenty patients (28.9%), all in PR or PD as the best response to HDC, underwent surgery of residual tumor: resection was complete in 17 patients and incomplete in 3; unfortunately, histologic findings, i.e. residual viable tumor, were not available. Among patients with complete resection of residual tumor, 10 are long-term survivors without tumor recurrence, 6 relapsed, and 1 was lost to follow-up. All patients with an incomplete surgery died of the progression of their disease.

Transplant-related mortality (TRM) occurred in three patients (4.3%), after a median of 13 days after transplant, in two for infectious complications and one for multiorgan failure; one patient died at day +71 from rapid PD.

DISCUSSION

The role of HDC in PMGCTs remains controversial mainly due to the lack of well-defined prognostic variables, and the limited number of studies reported in the literature. In this paper, we report the results of HDC in PMNSGCTs in patients reported in the EBMT database. To our knowledge, this is the largest series in this setting.

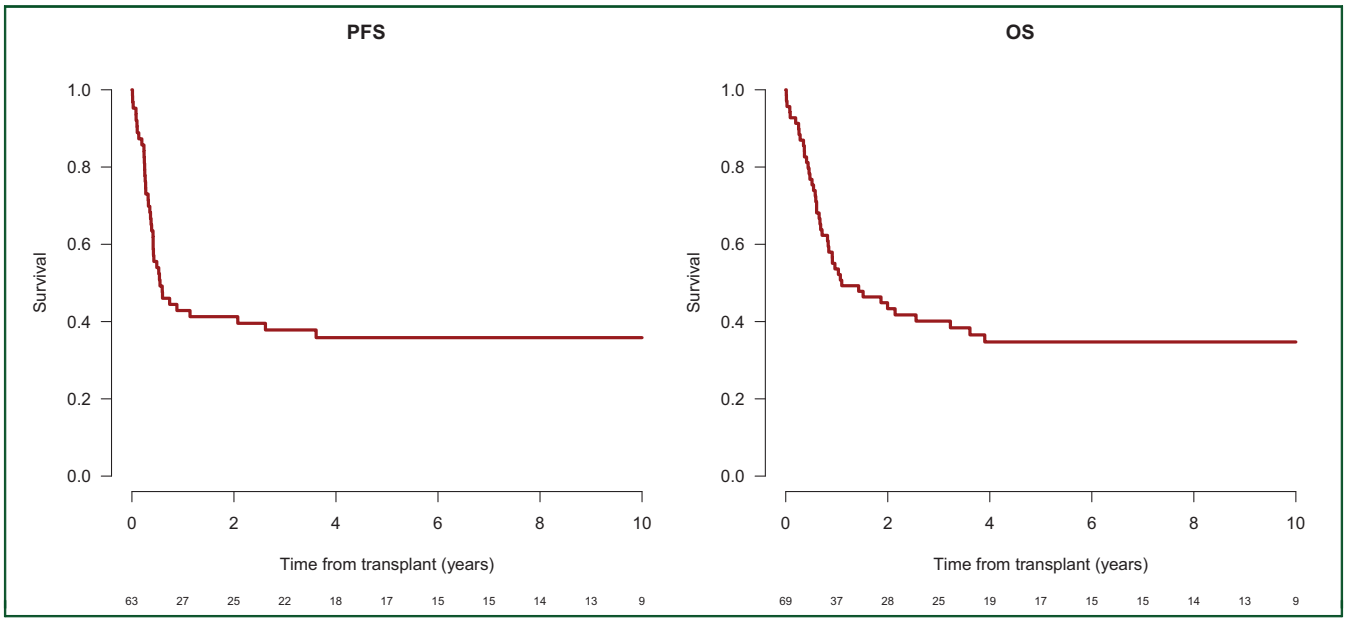

Figure 1. Progression-free survival and overall survival for 69 PMGCTs patients.
OS, overall survival; PFS, progression-free survival.

Among previously reported studies investigating the role of HDC for poor-prognosis GCT patients, PMNSGCTs usually represent a small subpopulation rarely discussed or assessed separately.[12]

Bokemeyer et al.[14] reported a subgroup of 28 patients with PMNSGCTs, who received upfront-line sequential high-dose VIP chemotherapy. Two-year PFS and OS rates suggested a 15%-20% absolute improvement in survival compared to conventional CT. Other studies in the first-line setting[15,16] did not provide clear information also because of the low number of patients and the use of HDC regimens not based on the carboplatin-etoposide doublet-triplet, the most consolidated and effective treatment modalities in GCTs.[11,17]

Also in the setting of relapsed disease, data from prospective and retrospective analyses are sparse and do not allow any conclusion on the potential benefit of HDC. Pico et al.[18] published a prospective trial of HDC as a salvage treatment for patients who relapsed to first-line platinum-based therapy. Among 280 enrolled patients, 25 of them were diagnosed with PMGCTs: 12 patients received a single course of HDC containing carboplatin/etoposide and cyclophosphamide while 13 patients underwent conventional-dose CT. The OS was 22% with no difference in survival between the two arms, but no conclusions can be drawn considering the limited number of patients.

In the early retrospective American and European study of relapsed poor-prognosis extragonadal GCTs,[19] 79 were PMGCTs: 54 patients received conventional CT and 25 patients were treated with tandem HDC. The OS rate after HDC was 12% and it did not differ from the results of standard-dose salvage treatment.

Similar results were reported by a previous retrospective EBMT study with a 3-year OS rate of 14% in 22 patients with PMNSGCTs, who received high-dose chemotherapy (HCT) between 1987 and 1999.[19] Nearly 75% of patients underwent a single course of HDC, compared with only 4.7% in our series. The vast majority of our patients underwent multiple HDC programs, which may well be a reason for the more favorable results observed in our study. It is also worth noting that early studies[19,20] included patients receiving bone marrow as a source of stem cells, while all patients in our series received peripheral blood stem cell (PBSC). Over the years, the switch from bone marrow to PBSC allowed for rapid delivery of the second/third course of HDC and improved outcomes in patients with PMNSGCTs.[21]

In the most recent Memorial Sloan-Kettering Cancer Center[19] and Indiana University[22] reports, of 21 and 32 patients with platinum-resistant PMNSGCTs, the long-term disease-free survival was 24% and 28%, respectively. In both studies, patients had a triple or double course of HDC with carboplatin and etoposide with PBSCT.

In our study, 24 patients (34.8%) underwent HCT upfront, and survival rates were similar to the largest upfront sequential chemotherapy with ASCT,[14] as 56.2% and 51.8% were disease free at 2 and 5 years, respectively. Among 45 patients who received HDC for recurrent or refractory diseases in our series, 25% can be possibly considered cured as no signs of recurrence exceeds 5 years.

In keeping with previous reports in GCTs and other diseases,[23,24] we show a more favorable outcome among patients with chemosensitive disease, as nearly 50% of patients transplanted in CR or PR were disease free at 5 years.

In our series 20 patients underwent post-HDC residual tumor resection. Despite the limited number of patients and the lack of histologic findings, our results suggest that surgery should be considered in selected patients.

Any potential benefit in survival must be weighed against the greater toxicities of HDC. In our series, TRM occurred in

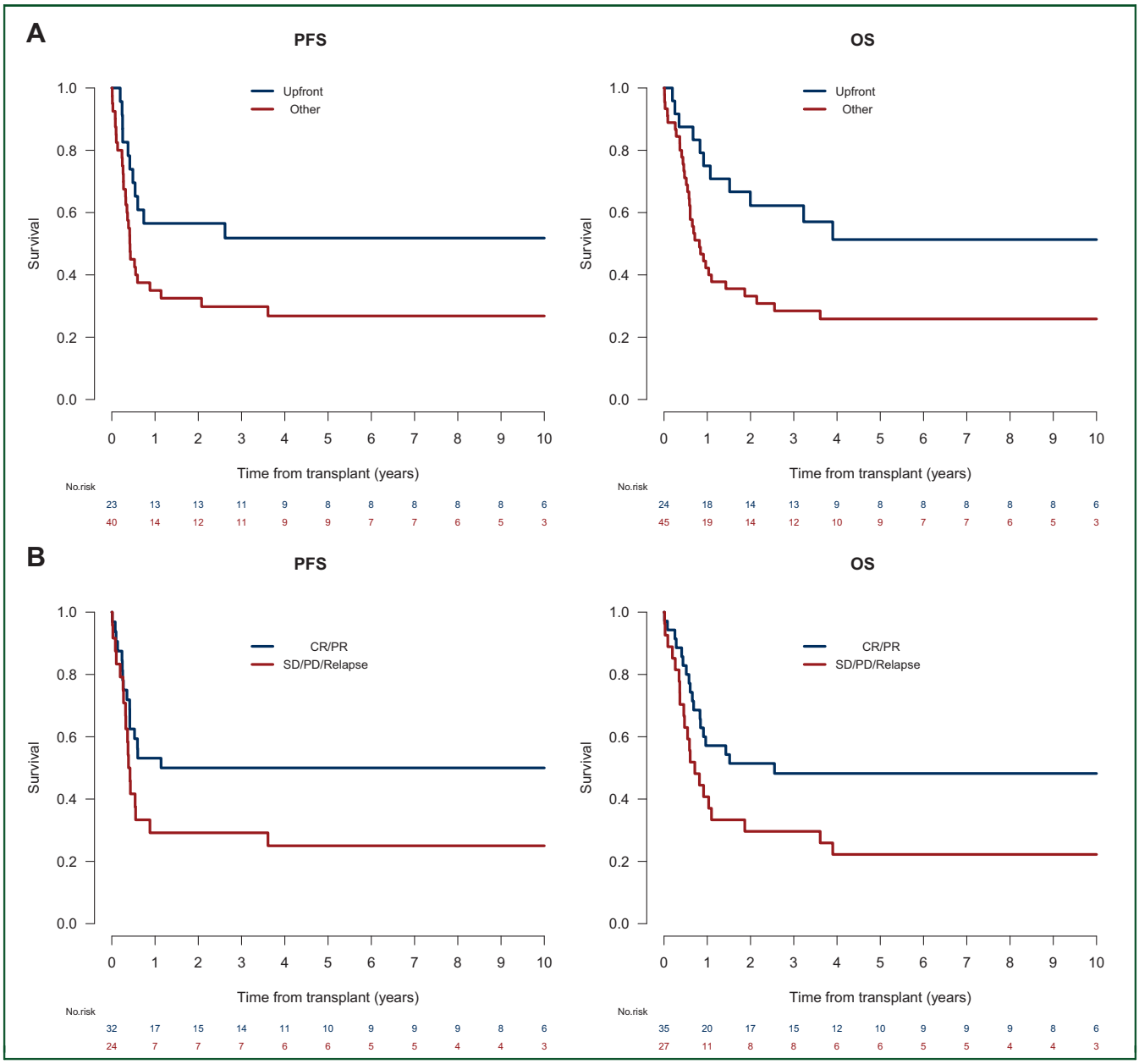

Figure 2. Progression-free survival and overall survival according to line of therapy (upfront versus other lines) (A) and according to status at transplant (B). CR, complete response; OS, overall survival; PD, progression disease; PFS, progression-free survival; PR, partial response; SD, stable disease.

three patients, and no secondary malignancies were recorded yet.

Our study suggests that HDC with ASCT is safe and represents a therapeutic option in patients with advanced PMNSGCTs. The optimum time of therapy and patient selection based on prognostic characteristics are issues to be further defined.

Strengths and limitations

To our knowledge, this is the largest series of HDC with ASCT in PMNSGCT patients and the first to thoroughly investigate potential predictors of benefit from this treatment. In addition, the long follow-up was capable of estimating long-term outcome in this rare disease. The limitation of our paper consists of the lack of a control group, due the retrospective nature of the study.

Conclusions

While we wait for effective biological therapies[25] in the still orphan setting of GCTs,[26] our results suggest that HDC with ASCT may well represent a therapeutic option in PMNSGCTs for second and further treatment lines or possibly as a front-line program. Patients with advanced disease (preferably at first diagnosis) should be referred for treatment decisions wherever possible to experienced centers.

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DISCLOSURE

The authors have declared no conflicts of interest.

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