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ORIGINAL ARTICLE

Prognostic impact of progression to induction chemotherapy and prior paclitaxel therapy in patients with germ cell tumors receiving salvage high-dose chemotherapy in the last 10 years: a study of the European Society for Blood and Marrow Transplantation Solid Tumors Working Party

A Necchi[1], R Miceli[1], M Bregni[2], C Bokemeyer[3], LA Berger[3], K Oechsle[3], K Schumacher[4], E Kanfer[5], JH Bourhis[6], C Massard[6], D Laszlo[7], J Montoro[7], A Flechon[8], F Arpaci[9], S Secondino[10], P Wuchter[11], P Dreger[11], M Crysandt[12], N Worel[13], W Kruger[14], M Ringhoffer[15], A Unal[16], A Nagler[17], A Campos[18], A Wahlin[19], M Michieli[20], G Sucak[21], I Donnini[22], R Schots[23], N Ifrah[24], M Badoglio[25], M Martino[26], D Raggi[1], P Giannatempo[1], G Rosti[27], P Pedrazzoli[10] and F Lanza[28] on behalf of the EBMT Solid Tumors Working Party

Little is known about the prognostic impact of prior paclitaxel therapy and response to induction chemotherapy defined as the regimen preceding high-dose chemotherapy (HDCT) for the salvage therapy of advanced germ cell tumors. Twenty European Society for Blood and Marrow Transplantation centers contributed data on patients treated between 2002 and 2012. Paclitaxel used in either prior lines of therapy or in induction-mobilization regimens was considered. Multivariable Cox analyses of prespecified factors were undertaken on PFS and overall survival (OS). As of October 2013, data for 324 patients had been contributed to this study. One hundred and ninety-two patients (59.3%) had received paclitaxel. Sixty-one patients (19%) had a progression to induction chemotherapy, 234 (72%) a response (29 (9%) missing or granulocyte colony-stimulating factor without chemotherapy). Both progression to induction chemotherapy and prior paclitaxel were significantly associated with shorter OS univariably ($P < 0.001$ and $P = 0.032$). On multivariable analysis from the model with fully available data ($N = 216$) progression to induction was significantly prognostic for PFS and OS ($P = 0.003$), but prior paclitaxel was not ($P = 0.674$ and $P = 0.739$). These results were confirmed after multiple imputation of missing data. Progression to induction chemotherapy could be demonstrated as an independent prognostic factor, in contrast to prior paclitaxel.

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INTRODUCTION

High-dose chemotherapy (HDCT) with hematopoietic stem cell support is a therapeutic option for germ cell tumors (GCTs) used since the late 1980s. It is a recognized therapeutic option in the salvage setting since the last few years, based on the results of two large retrospective series and a prospective clinical trial.[1–4] These studies showed that a large proportion of patients could be rescued by HDCT even if they had failed two or more chemotherapy regimens or in spite of yielding poor prognostic features. As a result, the number of HDCT performed in Europe has dramatically increased in the last years, up to the average of 550 transplants per year (corresponding to 260 patients/year) as it emerges from the European Society for Blood and Marrow Transplantation (EBMT) database (Figure 1).

Although there is much controversy about the role of dose-intensification in the first-salvage setting,[5] there are many fewer doubts in regards to the use of HDCT beyond the second-line whenever it is feasible. However, it is likely that the heterogeneity of these patients warrants a careful patient selection for HDCT with the aim to improve the outcomes. The International Prognostic Factor Study Group (IPFSG) classification is available for patients undergoing first-salvage chemotherapy.[6] Although response to prior chemotherapy has been included in this score as

[1]Fondazione IRCCS Istituto Nazionale dei Tumori, Milano, Italy; [2]Medical Oncology, Azienda Ospedaliera di Busto Arsizio, Busto Arsizio, Italy; [3]Universitätsklinikum Hamburg-Eppendorf, Hamburg, Germany; [4]UKGM-Marburg Klinik for Hematology and Oncology, Marburg, Germany; [5]Imperial College, Hammersmith Hospital, London, UK; [6]Gustave Roussy, Institut de cancérologie, Villejuif, France; [7]European Institute of Oncology, Milano, Italy; [8]Centre Léon Bérard, Lyon, France; [9]Gulhane Military Medical Academy, Ankara, Turkey; [10]Fondazione IRCCS Policlinico San Matteo, Pavia, Italy; [11]Universitätsklinikum Heidelberg, Heidelberg, Germany; [12]University Hospital of Aachen, Aachen, Germany; [13]University of Vienna, Vienna, Austria; [14]Universitätsmedizin, Greifswal, Germany; [15]Klinikum Karlsruhe gGmbH, Karlsruhe, Germany; [16]Kapadokya BMT Center, Kayseri, Turkey; [17]Chaim Sheba Medical Center, Tel-Hashomer, Israel; [18]Instituto Português de Oncologia do Porto, Porto, Portugal; [19]Umea University Hospital, Umeå, Sweden; [20]Centro di Riferimento Oncologico, Aviano, Italy; [21]Gazi University of Medicine, Ankara, Turkey; [22]University Hospital of Careggi, Firenze, Italy; [23]Universitair Ziekenhuis, Brussel, Belgium; [24]Centre Hospitalier Universitaire (CHU), Angers, France; [25]EBMT Study Office, EBMT, Paris, France; [26]Azienda Ospedaliera BMM, Reggio Calabria, Italy; [27]Ospedale Ca' Foncello, Treviso, Italy and [28]Istituti Ospitalieri di Cremona, Cremona, Italy. Correspondence: Dr A Necchi, Department of Medical Oncology, Fondazione IRCCS Istituto Nazionale dei Tumori Via G. Venezian 1, Milano 20133, Italy.
E-mail: andrea.necchi@istitutotumori.mi.it
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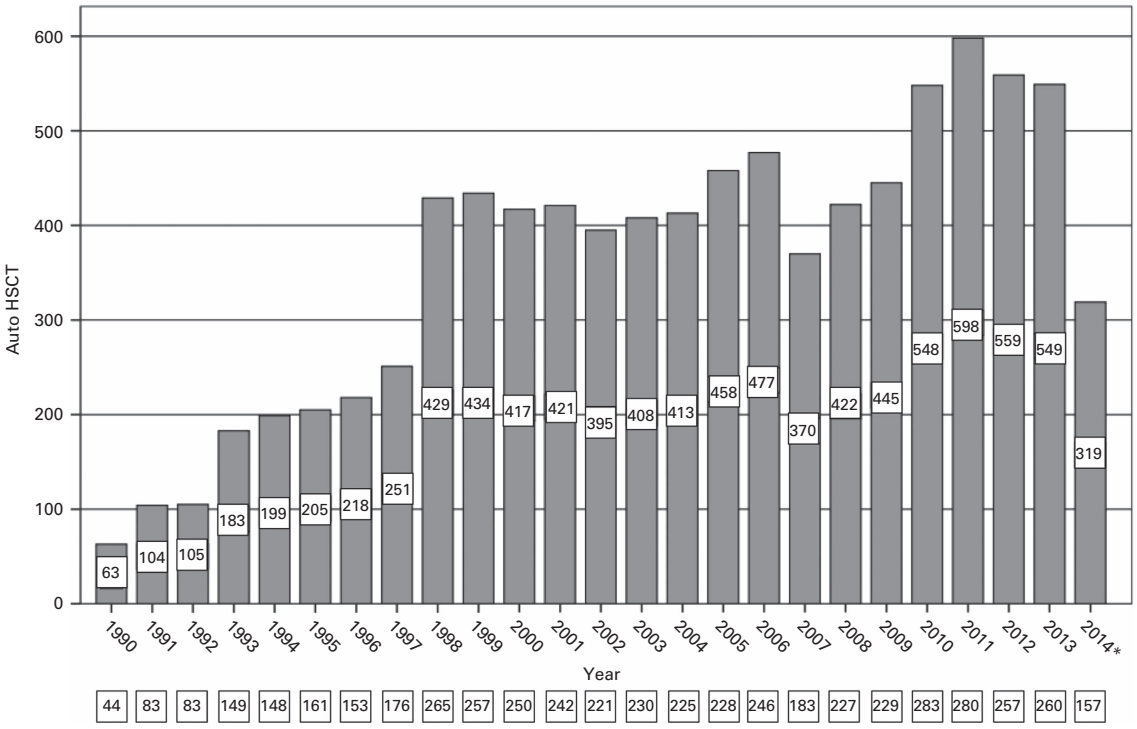

Figure 1. Number of high-dose chemotherapy courses (within the column) and transplanted patients (bottom) for germ cell tumor per year. *Complete data not yet available for 2014. A full color version of this figure is available at the *Bone Marrow Transplantation* journal online.

well as in other series,[1,7] that of response to induction/mobilization regimen preceding single or multiple HDCT cycles is unknown. Moreover, paclitaxel-based regimens are now commonly employed for second- or third-line salvage therapy of GCT,[8] and their prognostic impact on the results of subsequent salvage HDCT in these patients is unknown as well.

The objective of this retrospective study was to evaluate the prognostic impact of response to induction chemotherapy administered as part of the HDCT strategy as well as of prior paclitaxel-containing chemotherapy. The hypothesis was that these additional factors might be useful to improve the available prognostic models and might be applied in prospective studies of HDCT.

PATIENTS AND METHODS

Study design and patient population

The number of transplants performed each year for GCT in the EBMT network currently relies on the minimum essential data-A forms. Unfortunately these forms, which are routinely centralized to EBMT offices from the certified centers, were not suitable for the purposes of the present study because of the lack of the vast majority of required clinical information. Hence, centers that were contributing data to EBMT were selected based on their expertise in GCT treatment. The principal selection criterion was 20 patients treated with HDCT in the last 10 years. Principal investigators from these centers were asked to fill in uniform data fields, comprising baseline characteristics and pathology information, induction/mobilization treatments, and HDCT regimen using a study-specific Excel sheet, after approval of each institutional review board and ethics committee. Quality control and check for consistency were made by the EBMT Office in Paris. Inclusion criteria for the current analysis were the following: the administration of salvage HDCT between the years 2002 and 2012, male gender, minimum age of 18 at first transplant, either gonadal or extragonadal origin, administration of induction chemotherapy before HDCT (i.e. cases who were mobilized without chemotherapy were excluded), the administration of paclitaxel in any lines before HDCT. The use of paclitaxel in induction regimens before HDCT was also included. Induction chemotherapy was referred to as any regimen administered with debulking and/or mobilization purposes whenever HDCT was planned. Patients were defined as responders if they had achieved at least stable disease (that is, CR, partial response with normal/normalized markers (PRm-), partial response with markers still elevated (PRm+) or stable disease) or as having a progression to induction otherwise. CR was defined as no clinically or radiographically detectable disease and normal/normalized serum tumor markers. Disease progression was defined as growing non-teratomatous masses or an increase of serum tumor marker. Chemosensitivity was defined according to the response to the lines of therapy preceding HDCT and following the conventional definition in use: disease was considered cisplatin refractory when at least a tumor stabilization or a remission had been achieved, but progression occurred again within 4 weeks of the last cisplatin administration. Disease progressing during chemotherapy was defined as absolute refractoriness.[7,9]

Statistical analysis

The main study end points were PFS and overall survival (OS). OS was defined as the time between the start of first HDCT and death from any cause; time was censored at the date of last follow-up for patients remaining alive. PFS was the time between the start of first HDCT and the date of disease progression or death without progression, whichever occurred first; time was censored at the date of last follow-up for patients alive without progression. PFS and OS curves were estimated with the Kaplan–Meier method and the log-rank test was used for subgroup comparison. Multivariable analyses based on Cox regression models were also undertaken to evaluate the prognostic association between OS and PFS and the following prespecified prognostic covariates: year of transplant, primary tumor site, International Germ Cell Cancer Collaborative Group (IGCCCG) risk category,[10] chemosensitivity, number of prior chemotherapy regimens, response to induction chemotherapy, paclitaxel-based chemotherapy before HDCT and taxane-based HDCT regimen.

Some covariates presented with missing data and this reduced the complete data set for model fitting. As a consequence, the number of events was lowered, and although for the PFS model it was still adequate to the degrees of freedom (d.f.) according to the Peduzzi's strategy,[11] for OS the number of deaths was slightly lower the cutoff of 10 per d.f. Thus, in addition to the analysis on the subset of patients with complete data, we decided to fill covariate missing data by applying a multiple imputation method (MI) according to Clark and Altman[12] and applied the MICE

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method.[13] We generated 50 completed data sets; the MI models contained all the covariates, together with the log-cumulative hazard of death and progression (details on request).

The binary associations between the covariates were tested using the exact χ^2 test. The association between response to induction chemotherapy and the transplant setting (that is, number of prior chemotherapy regimens) was also investigated in a multivariable logistic regression model, with adjustment for the other covariates; missing values were assigned to an additional category. The statistical analyses were performed using the SAS and R software (Institute for Statistics and Mathematics of WU (Wirtschaftsuniversität), Wien, Austria; the R Project for Statistical Computing. http://www.r-project.org/, last access 15 April 2015). We considered a statistical test as significant when the corresponding *P*-value was $< 5\%$.

RESULTS

Patient characteristics and treatment

As of October 2013, 324 patients from 20 centers and 7 countries contributed data on either response to induction chemotherapy or prior taxanes (Supplementary Table 1). Characteristics of patients, disease and treatments are summarized in Table 1. The median age of the cohort was 33 years (interquartile range (IQR): 26–40), the majority of cases (137, 42.3%) had a poor risk disease at the GCT diagnosis, and 159 patients overall (49.1%) had received HDCT in the third-line setting or beyond. Overall, 192 (59.3%) had received paclitaxel and 61 (18.8%) had a disease progression to induction chemotherapy. Seventy-six patients (23.4%) had received taxane-containing HDCT, consisting of paclitaxel in 70 patients and docetaxel in six patients only.

Response, survival and prognostic factors

Overall, 175 patients (54.0%) achieved a CR or PRm- to HDCT and 75 (23.2%) were surgically resected after HDCT (25 (33.3%) yielding fibrosis and necrosis). No significant association was found between prior paclitaxel and response (that is, CR/PRm-) to HDCT ($P = 0.811$). Response to induction chemotherapy was significantly associated to response to HDCT ($P < 0.001$), and to the number of prior lines of therapy preceding HDCT both univariably ($P = 0.001$) and multivariably ($P = 0.031$, Supplementary Table 2).

Median follow-up was 36 months (IQR: 19–70). Overall, 179 patients had a progression and 150 died. Two-year PFS of patients who had a response to induction chemotherapy was 42.4% (95% confidence interval (CI): 36.3–49.5), whereas it was 22.5% (95% CI: 13.9–36.4) for those who had a progression to induction ($P < 0.001$, Figure 2a). Two-year OS was 58.7% (95% CI: 52.2–66.0) and 31.9% (95% CI: 21.6–47.1), respectively ($P < 0.001$, Figure 2b). Two-year PFS of patients who had received paclitaxel before HDCT was 35.2% (95% CI: 28.9 to 42.9), whereas it was 40.9% (95% CI: 33.1–50.5) for those who had not ($P = 0.182$, Figure 2c). Two-year OS was 49.9% (95% CI: 42.8–58.2) and 58.8% (95% CI: 50.5– 68.5), respectively (hazard ratio (HR): 1.44, 95% CI: 1.03–2.01, $P = 0.034$, Figure 2d). PFS and OS curves in the population obtained when excluding taxane-based HDCT ($N = 248$) are provided as Supplementary Figures 1a and b ($P = 0.087$ and $P = 0.018$, respectively). Clinical outcome according to the line of HDCT is shown in Figures 3a and b. In particular, 2-year PFS was 43.9% (95% CI: 36.7–52.6), 35.2% (95% CI: 26.9–46.1) and 23.8% (95% CI: 14.9–38.1) in the second-line, third-line and beyond the third-line, respectively.

Results of the multivariable analyses for PFS are shown in Table 2. In the model with fully available data ($N = 216$) the primary tumor site (overall $P = 0.043$), IGCCCG category (overall $P = 0.048$), and progression to induction chemotherapy (HR: 1.92, 95% CI: 1.24–2.98, $P = 0.003$) were significantly prognostic, and results were largely confirmed in the model with MI of missing data. For OS, IGCCCG category (overall $P = 0.048$), taxane-based HDCT (HR: 2.61, 95% CI: 1.18 –5.76, $P = 0.017$) and progression to induction chemotherapy (HR: 2.09, 95% CI: 1.27–3.42, $P = 0.003$) were significant predictors (Table 3). Results were confirmed for the latter in the model with MI of missing data.

Table 1. Patient and disease characteristics pre-HDCT

	No.	*%*
Total number of patients	324	-
Transplant period	2002–2012	
Age (median, IQR): years	33 (26–40)	
Tumor primary site		
Gonadal	240	74.1
Mediastinal	27	8.3
Retroperitoneal	39	12.0
Other unspecified	11	3.4
Missing data	7	2.2
Histology		
Pure seminoma	39	12.1
Nonseminoma or mixed germ cell tumors	258	79.6
Missing data	27	8.3
IGCCCG prognostic category		
Good prognosis	55	17.0
Intermediate prognosis	47	14.5
Poor prognosis	137	42.3
Missing data	85	26.2
Disease chemosensitivity before mobilization		
Refractory/absolutely refractory	110	34.0
Chemosensitive	211	65.1
Missing data	3	0.9
Transplant setting		
Second-line	165	50.9
Third-line	102	31.5
Beyond third-line	57	17.6
Paclitaxel-based chemotherapy before HDCT		
Yes	192	59.3
No	132	40.7
Response to induction/mobilization chemotherapy		
Response/stable disease to induction	234	72.2
Progression to induction	61	18.8
Not applicable (GCSF only)	22	6.8
Missing data	7	2.2
First mobilization regimen		
Cisplatin-etoposide-Ifosfamide	93	28.7
Paclitaxel-Ifosfamide	50	15.4
Etoposide	52	16.0
High-dose cyclophosphamide	7	2.2
Epirubicin-paclitaxel	19	5.9
Ifosfamide-carboplatin-etoposide	20	6.2
Paclitaxel-Ifosfamide-cisplatin	26	8.0
Other mixed regimens	34	10.5
GSCF only	22	6.8
Missing data	1	0.3
High-dose chemotherapy regimen		
CE	177	54.6
CEI	41	12.7
CarboPEC	20	6.2
Taxane-containing (paclitaxel, docetaxel) HDCT	76	23.4
Other	10	3.1

Abbreviations: CarboPEC = carboplatin, etoposide, cyclophosphamide; CE = carboplatin, etoposide; CEI = carboplatin, etoposide, ifosfamide; GCSF = granulocyte colony-stimulating factor; HDCT = high-dose chemotherapy; IGCCCG = International Germ Cell Cancer Cooperative Group; IQR = interquartile range.

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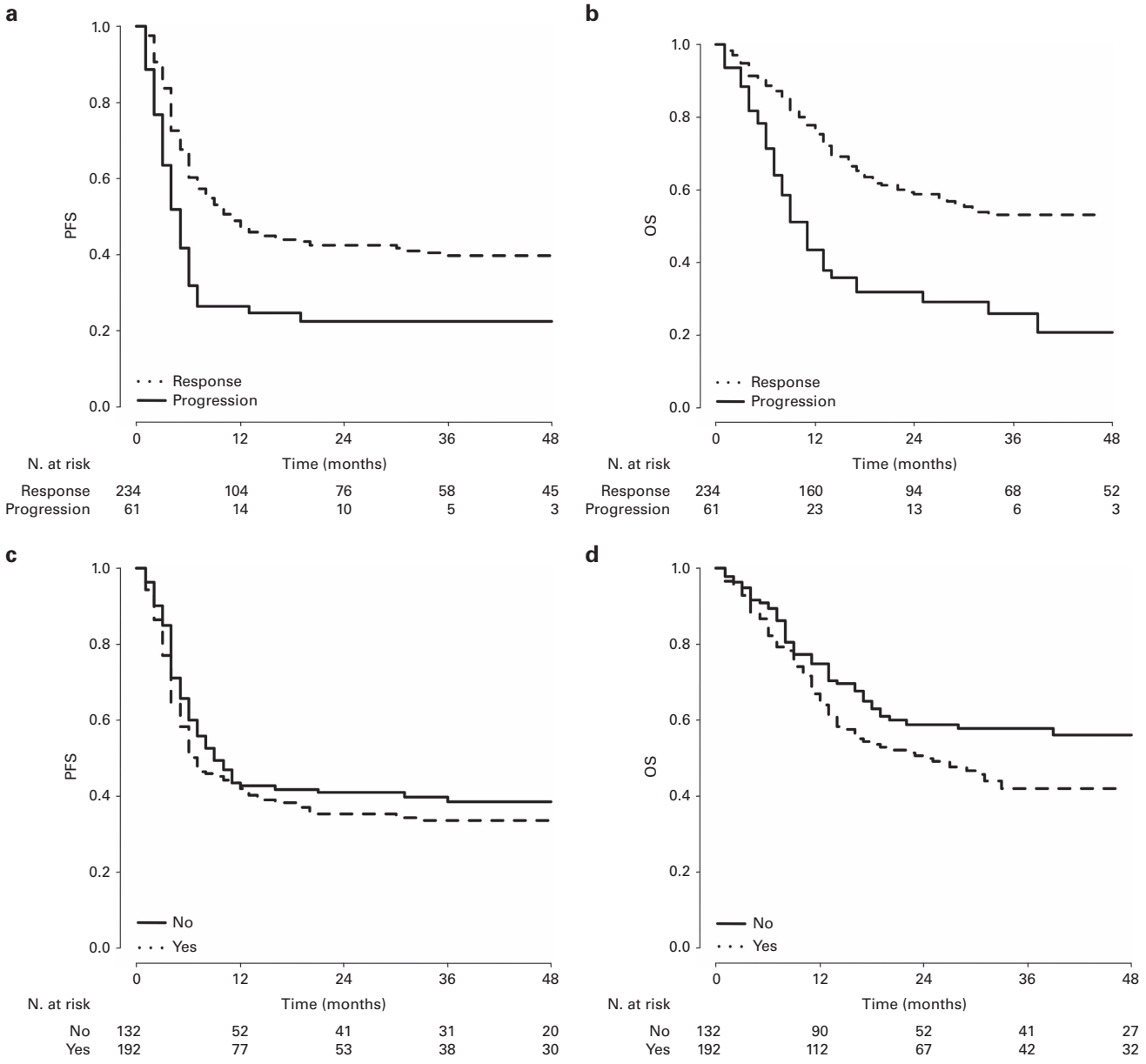

Figure 2. (**a**) Kaplan–Meier curves of PFS according to response to induction chemotherapy. Legend: continuous line: progression; dotted line: response. (**b**) Kaplan–Meier curves of overall survival according to response to induction chemotherapy. Legend: continuous line: progression; dotted line: response. (**c**) Kaplan–Meier curves of PFS according to prior paclitaxel chemotherapy. Legend: continuous line: no; dotted line: yes. (**d**) Kaplan–Meier curves of overall survival according to prior paclitaxel chemotherapy. Legend: continuous line: no; dotted line: yes.

DISCUSSION

The current analysis attempted to address the prognostic impact of two potentially useful factors in the clinical care of patients with GCT receiving salvage HDCT. Although the prior administration of paclitaxel was significantly prognostic for OS at univariable analysis, it was not significant at the multivariate level. It is likely that the univariable result was partly influenced by the possibility to administer more active salvage therapies to taxane-free patients after failure of HDCT, but details about the subsequent therapies beyond progression to HDCT have not been captured in this database. Most importantly, progression to induction chemotherapy consistently emerged as a detrimental factor on both PFS and OS after HDCT.

Among the patients selected for the analysis, missing data for the variables utilized in the multivariable analysis were not infrequent; however, the results were consistent across the models with full and imputed data.

Owing to the unavailability of relevant clinical information for all transplanted patients in the EBMT framework, the selection bias that might have resulted from the present study is a concern that cannot be fully addressed. However, in order to minimize the risk of such a bias, a selection of centers based on their expertise in GCT was made, assuring that these centers are currently following or contributing to make international guidelines in this disease. Also, the baseline characteristics of the analyzed cohort were those typical of relapsed GCT patients.

Other potentially confounding factors should be acknowledged: first, the detrimental effect of progression to induction chemotherapy could be assessed only in patients who actually had received HDCT from this database, but a proportion of patients

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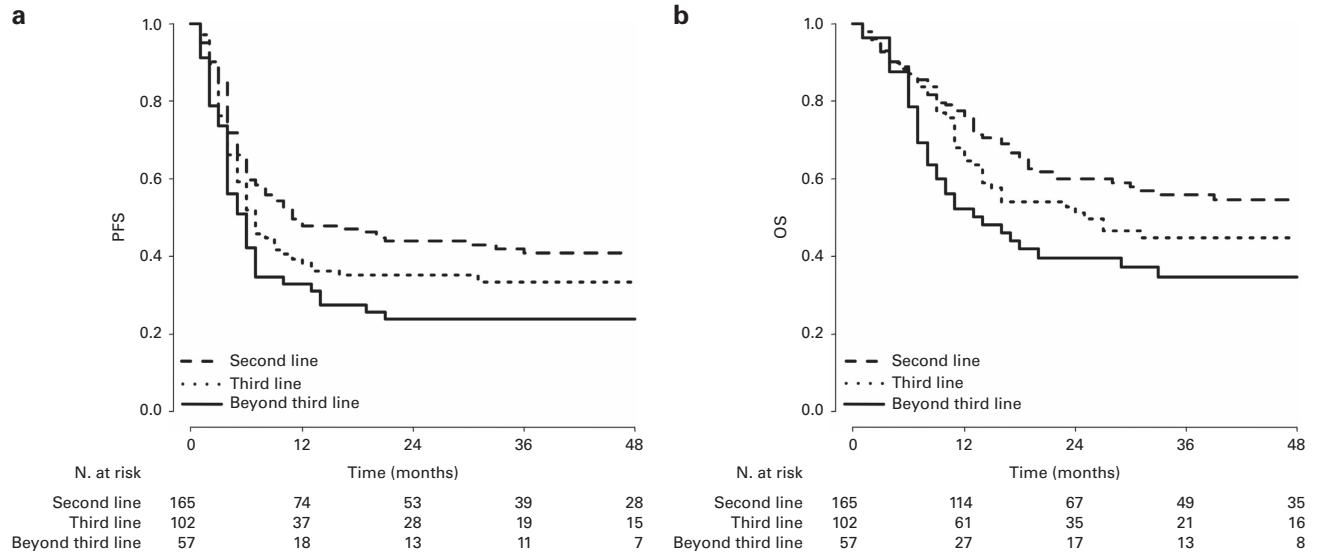

Figure 3. (**a**) Kaplan–Meier curves of PFS according to the line of HDCT. (**b**) Kaplan–Meier curves of overall survival according to the line of HDCT.

Table 2. Results of multivariable Cox analyses of PFS

Factor	*Patients with full data (N = 216), model without MI*			*All patients (N = 324), model with MI*		
	HR	*95% CI*	P-*value*[a]	*HR*	*95% CI*	P-*value*[a]
Year of transplant			0.289			0.912
2008–2012 vs 2002–2007	0.77	0.47–1.25		0.98	0.68–1.41	
Tumor primary site			0.043			0.044
Gonadal vs retroperitoneal	1.44	0.83–2.49		1.19	0.76–1.86	
Mediastinal vs retroperitoneal	2.70	1.33–5.49		2.08	1.14–3.80	
Other vs retroperitoneal	1.19	0.32–4.52		0.67	0.26–1.78	
IGCCCG category			0.048			0.059
Intermediate vs good	1.22	0.68–2.19		1.29	0.79–2.10	
Poor vs good	1.76	1.08–2.86		1.65	1.07–2.52	
Disease chemosensitivity			0.668			0.536
Chemorefractory vs chemosensitive	0.92	0.63–1.34		1.11	0.80–1.52	
Transplant setting			0.338			0.138
3rd Line vs 2nd line	1.38	0.89–2.14		1.19	0.84–1.68	
>3rd Line vs 2nd line	1.35	0.72–2.50		1.52	1.01–2.29	
Response to induction chemotherapy			0.003			0.022
Progression vs response/stable disease	1.92	1.24–2.98		1.55	1.07–2.26	
Paclitaxel-based chemotherapy before HDCT			0.674			0.694
Yes vs no	1.10	0.70–1.73		1.07	0.77–1.49	
Taxane-containing HDCT			0.840			0.320
Yes vs no	1.07	0.55–2.07		1.25	0.81–1.94	

Abbreviations: CI = confidence interval; HDCT = high-dose chemotherapy; HR = hazard ratio; IGCCCG = International Germ Cell Cancer Cooperative Group; MI = multiple imputation of missing data. [a]*P*: two-sided Wald test *P*-value.

with disease progression have likely been excluded from HDCT. This is the reason why a disease progression to induction chemotherapy was reported in only a very small proportion of patients (18.8%). Second, the present analysis was lacking of a comparison with an alternative conventional-dose strategy, and we could not make any recommendation regarding the most effective treatment for patients with a chemoresistant disease. The assessment of chemoresistance provided here would need a prospective validation through a trial design similar to that of the Groupe d'Etude des Tumeurs Urogénitales-13 trial whereby the intensity of treatment (that is, dose-dense regimen vs standard chemotherapy) was based on the early assessment of the kinetics of tumor marker decline.[14] However, the number of available patients will hardly allow running such a study design in the salvage setting.

Third, patients who had not received any chemotherapy for mobilization or debulking purposes, and who had been mobilized with granulocyte colony-stimulating factors only (6.8%), were excluded from the study. Nevertheless, a few important observations can be made from the current analysis. Although there is a general agreement in favor of the use of HDCT in relapsing patients, available results should be critically reviewed according to chemoresistance, mostly referred to as either PD as best response to prior chemotherapy regimens or the inclusion into

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Table 3. Results of multivariable Cox analyses of overall survival

Factor	*Patients with full data (N = 216), model without MI*			*All patients (N = 324), model with MI*		
	HR	*95% CI*	P-*value*[a]	*HR*	*95% CI*	P-*value*[a]
Year of transplant			0.276			0.742
2008–2012 vs 2002–2007	1.45	0.74–2.81		1.07	0.70–1.65	
Tumor primary site			0.142			0.294
Gonadal vs retroperitoneal	1.58	0.79–3.20		1.07	0.64–1.79	
Mediastinal vs retroperitoneal	2.43	1.00–5.94		1.31	0.63–2.75	
Other vs retroperitoneal	0.43	0.05–3.64		0.34	0.09–1.33	
IGCCCG category			0.048			0.227
Intermediate vs good	1.07	0.54–2.11		1.29	0.74–2.23	
Poor vs good	1.51	0.86–2.67		1.53	0.94–2.48	
Disease chemosensitivity			0.229			0.047
Chemorefractory vs chemosensitive	1.31	0.84–2.04		1.46	1.01–2.13	
Transplant setting			0.340			0.167
3rd Line vs 2nd Line	1.39	0.81–2.38		1.23	0.82–1.85	
>3rd Line vs 2nd Line	1.65	0.80–3.40		1.57	0.98–2.52	
Response to induction chemotherapy			0.003			0.035
Progression vs response/stable disease	2.09	1.27–3.42		1.64	1.04–2.60	
Paclitaxel-based chemotherapy before HDCT			0.739			0.586
Yes vs no	1.09	0.64–1.86		1.12	0.75–1.66	
Taxane-containing HDCT			0.017			0.010
Yes vs no	2.61	1.18–5.76		1.88	1.17–3.04	

Abbreviations: CI = confidence interval; HDCT = high-dose chemotherapy; HR = hazard ratio; IGCCCG = International Germ Cell Cancer Cooperative Group; MI = multiple imputation of missing data. [a]*P*: two-sided Wald test P-value.

high-risk categories of the IPFSG classification. Despite the global favorable survival estimates, only a small proportion of patients with the above characteristics could be ultimately rescued according to the available series.[15] In clinical practice, response to induction chemotherapy, when applicable, could help to refine the prognostic ability of the available models and should be included in the guidance for patient selection and counseling as well. Results from subset analyses of large prospective trials will be able to corroborate the present findings and are required before incorporate response to induction chemotherapy as a prognostic factor for the next studies. The opening phase 3 study of conventional-dose chemotherapy (TIP: paclitaxel, ifosfamide and cisplatin) vs high-dose chemotherapy (TI-CE: paclitaxel and ifosfamide, followed by high-dose carboplatin and etoposide) as first-salvage therapy of GCT (TIGER trial) will serve as an ideal platform to this aim.

Unfortunately, we were unable to capture the information on the number of cycles of induction chemotherapy that had been administered in each case. This information is critical since, by definition, induction chemotherapy entails the administration of 1–2 cycles of standard dose chemotherapy for mobilization and debulking purposes. Nevertheless, the timing of HDCT delivery (that is, sequentially after the end of the induction course in each case) lends confidence to the reliability of response to induction chemotherapy as an independent prognostic factor that can be more impactful than response to the prior lines of chemotherapy.

Indeed, the timing of response assessment before HDCT has emerged as the most critical prognostic factor in GCT. Although we have not recorded how progression to induction chemotherapy has been assessed in each case, it is likely that it was based on rising serum tumor marker only in most cases. Rising serum tumor marker during induction chemotherapy is an important parameter of reduced efficacy of HDCT to be considered. In parallel, we were able to provide an updated outcome assessment of HDCT in the salvage setting of GCTs. We collected a large number of patients who have been given HDCT in the community framework, that is, outside of clinical trials or single institution series for this disease. Although the outcomes in the second-line setting paralleled those obtained in a recent retrospective study,[2] we were also able to analyze the outcome beyond the second-line setting ($N = 159$), an area for which available results are biased by limited numbers.

More than one-third of patients who had received HDCT in the third-line benefited from a sustained PFS, and up to 24% of those who had received HDCT beyond the third-line. Among these patients, long-term OS was 45% in the third-line and 35% beyond the third-line. These results do confirm those obtained in the cohort of 49 patients who had been treated with tandem high dose (HD)-carboplatin and etoposide in the third-line or beyond at the Indiana University.[1]

In conclusion, in this analysis we observed that the results of HDCT as salvage therapy administered in the last 10 years were not influenced by the increasing use of paclitaxel-containing salvage chemotherapy preceding HDCT. Most importantly, we have observed a significant negative prognostic impact of disease progression to induction chemotherapy that may justify why a number of such patients are not administered HDCT in clinical practice.

Globally, HDCT (namely tandem or triple cycle of HD-carboplatin and etoposide) confirms to be a substantially effective strategy once one or multiple chemotherapy regimens have failed.

AUTHOR CONTRIBUTIONS

The study conception and design were made by AN; the study did not received any financial support; all authors collected and assembled the data; data analysis and interpretation were done by AN, RM, PP, FL; all authors wrote and approved the final version of the manuscript.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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