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LETTER TO THE EDITOR

Administration of high-dose chemotherapy with stem cell support in patients 40 years of age or older with advanced germ cell tumours: a retrospective study from the European Society for Blood and Marrow Transplantation database

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Germ cell tumours (GCT) comprise exquisitely chemosensitive neoplasms, and cure is possible in patients presenting with a high metastatic tumour burden. For the few patients with high-risk disease or who relapse after first-line chemotherapy, the administration of a tandem or a triple course of high-dose chemotherapy (HDCT) with carboplatin and etoposide with stem cell support may represent a valuable therapeutic option.[1–3] Although GCT remains the most frequent solid tumour in young adults, evidence of a shift towards older age at diagnosis has been reported by many authors.[4] Furthermore, increasing age at diagnosis has been reported to have a poor prognostic effect in GCT patients receiving first-line chemotherapy.[5–7] In a large study by Danish authors and another double-institution dataset, age was identified as a statistically significant poor prognostic factor in multivariable analyses. For this reason, it is possible that older patients with GCT have an inherently negative prognostic factor related to their age, which may partly explain the inability to administer timely curative chemotherapy in some cases due to the haematological toxicity of bleomycin, etoposide, and cisplatin (BEP) chemotherapy.[8–12]

In general, for patients aged 40 years or older, there are concerns regarding the possibility of administering standard chemotherapy in a timely manner and preserving the full dose of all drugs throughout the treatment course. In the case of HDCT administration, limited data are available for older GCT patients, and the benchmark safety data can be transferred from haematologic neoplasms. Obtaining robust information that HDCT can be safely administered in this patient population may help clinicians in the decision-making process and patient counselling, given the uncertainties regarding the optimal salvage therapeutic strategy.

For this reason, we conducted a retrospective study on the database of the European Society for Blood and Marrow Transplantation (EBMT)—Solid Tumors Working Party (STWP). The study aimed to analyse the incidence of severe side effects following HDCT administration in patients aged more than 40 years at the time of first HDCT course. Statistical analyses relied on transplant-related mortality (TRM) as the primary endpoint. Summary statistics were used to describe patient characteristics and outcomes, and the reverse Kaplan–Meier method described by Schemper and Smith was used for follow-up quantification.[13] TRM was defined as mortality from any cause other than disease progression within 100 days of HDCT. Logistic multivariable models were constructed with the following variables: treatment period (1981–1989; 1990–1999; 2000–2015), age, conditioning regimen type and stem-cell source. Multiple imputation was used to account for the missing data, and supportive analyses were performed through the complete-case data set. Statistical analyses were performed with SAS (version 9.2, SAS Institute, Cary, NC, USA) and R software (version 3.2.3, R Foundation for Statistical Computing, Vienna, Austria). Statistical significance was set at the conventional 5% two-sided threshold.

From November 1981 to December 2015, 1179 patients aged ⩾40 years were identified from a total of 5295 registered patients (22%) from 226 EBMT centres. The median follow-up was 36.6 months (interquartile range: 9.3–99.5 months). The flow of patient selection is described in Supplementary Figure 1. A total of 1169 patients with the suitable data were included in the final analyses. The distribution of the main baseline characteristics is provided in Supplementary Table 1, together with their TRM rate. There were 909 patients aged 40–49, 234 aged 50–59 and 26 cases aged
60 years or older. HDCT consisted of the administration of carboplatin and etoposide in 382 patients, whereas 349 patients received mixed HDCT regimens (the information was not available in 438 cases). Table 1 provides subgroup analyses on the TRM rate according to the combination of the main factors. In this case, treatment period was split in 1981–1999 and 2000–2015 due to the small numbers. The highest TRM rate was noted in the earliest period, as expected (12.5%), but very few HD-carboplatin-etoposide courses were administered in this period. Most of the cases received HD-carboplatin and etoposide in the years 2000–2015, in which the TRM rate was 3.2%. In addition, TRM with this regimen ranged from 2.5 to 3.5% across the age subgroups (data not shown).

Results of the logistic multivariable model are provided in Table 2 after multiple imputation of missing data. Notably, only the type of conditioning regimen (i.e., carboplatin-etoposide HDCT regimen vs other) was significantly associated with TRM

Table 1. Subgroup analysis for transplant-related mortality of patients with advanced GCT according to the combination of treatment period and conditioning regimen

Treatment period	*Conditioning regimen*	*TRM*			
		No		*Yes*	
		N	%	N	%
1981–1999	CBDCA-VP16	6/6	100.0	—	—
	Mixed	84/96	87.5	12/96	12.5
	NA	144/155	92.9	11/155	7.1
2000–2015	CBDCA-VP16	364/376	96.8	12/376	3.2
	Mixed	234/253	92.5	19/253	7.5
	NA	263/283	92.9	20/283	7.1
Total		1095/1169	93.7	74/1169	6.3

Abbreviations: CBDCA = carboplatin; GCT = germ cell tumours; NA = not available; TRM = transplant-related mortality; VP16 = etoposide.

Table 2. Logistic multivariable model to analyse the association of main factors with TRM, after multiple imputation of the missing data

Factor	*Odds ratio*	*95% CI*	P-*value*[a]
Treatment period:			0.763
1990–1999 vs 1981–1989	0.64	0.14–2.80	
2000–2015 vs 1981–1989	0.69	0.14–3.54	
Age:			0.551
50–59 vs 40–49	0.70	0.36–.37	
60+ vs 40–49	1.22	0.28–5.40	
Conditioning regimen:			0.024
CBDCA-VP16 vs mixed	0.40	0.18–0.89	
Stem cell source:			0.319
BM vs PB	1.60	0.73–4.04	

Abbreviations: BM = bone marrow; CBDCA = carboplatin; CI = confidence interval; PB = peripheral blood hematopoietic stem cells; TRM = transplant-related mortality; VP16 = etoposide. [a]Two-sided Wald's test *P*-value.

(odds ratio: 0.40, 95%CI: 0.18–0.89, $P = 0.024$). The same results were obtained in the complete-case multivariable analyses (Supplementary Table 2).

The main causes of TRM are presented in Supplementary Table 3. As noted, the majority of patients (28.4%) died from infections and the development of septic shock in addition to other cases who died as a consequence of organ failure or haemorrhage.

To our knowledge, we present one of the largest studies on the incidence of TRM in patients receiving HDCT after the age of 40 regardless of the tumour type. Additionally, we provide the first study of this type focusing on GCT patients. The evidence clearly corroborates the feasibility of the preferred modern approach that favours the administration of multiple courses of HD-carboplatin and etoposide in the very rare population of older patients. Interestingly, in the largest European registry of HDCT, 23.1% of patients with GCT received treatment with at the age of 40 years or older, representing a significant number of patients among those who received autologous transplantation for GCT. This information was mostly unknown to us prior to the present analysis. Of course, some biases should be accounted for when interpreting the findings, which are mainly attributable to the limits of retrospective, long-dated analyses. First, and most importantly, we could not finely analyse the tolerability of HDCT administration, for example, by including the additional data on the incidence of severe acute and long-term side effects, given the lack of suitable data. Second, we did not have information regarding the number of chemotherapy regimens administered in each case prior to HDCT. This information may be important as the burden of prior chemotherapies is likely to negatively affect the TRM risk; however, the rate of TRM after carboplatin and etoposide was generally less than 4%. The incidence of 2.5–3.5% TRM is consistent with the reported results from a large series of HDCT in younger GCT patients using the same conditioning regimen. Therefore, the administration HD-carboplatin and etoposide does not seem to be associated with an excess risk of TRM in older patients, which is also evident from the multivariable analyses. Third, findings that are applicable to the current practice are ultimately those reported in the period 2000–2015 ($n = 912$), when the majority of patients received both modern chemotherapy and modern best supportive care. In addition, peripheral blood haematopoietic stem cells were used in all cases.

In general, for older patients with GCT, concerns may be raised about the possibility of administering standard chemotherapy in a timely manner and preserving the full dose of all drugs in each cycle. In a retrospective analysis from the United States, the data on conventional-dose chemotherapy in these patients were reported. In total, 236 patients aged $\geqslant 50$ years were treated, and significant rates of neutropenic fever and haematological severe toxicities were observed after BEP chemotherapy.[11] Dose reductions, delays or treatment change were required in 30 patients. Conversely, in another English study, the authors did not observe toxicity issues with the use of BEP chemotherapy in 60 patients who were older than 60 years.[12]

A comprehensive risk-benefit evaluation should include co-morbidities and the patient's risk category, and chemotherapy regimens may be tailored in some cases. The prognosis is poorer for older patients with nonseminoma histology. In the salvage setting, informed consent should comprise adequate information on the risks of severe toxicities from every treatment modality, including HDCT. On the basis of our large retrospective analysis, patients without any significant comorbidity contraindicating HDCT administration should be aware that the mortality risk due to transplant is similar to that of younger patients, ranging from 2.5 to 3.5%.

In conclusion, the present data may aid physicians who are treating advanced GCT to improve their knowledge of the mortality-rate after HDCT administration in older patients. HDCT can be safely administered in these high-risk patients and still represents their first therapeutic option in the salvage setting, pending prospective validation through clinical trials.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Supplementary Information accompanies this paper on Bone Marrow Transplantation website (http://www.nature.com/bmt)