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First-line high-dose chemotherapy for patients with poor prognosis extragonadal germ cell tumors: the experience of the European Bone Marrow Transplantation (EBMT) Solid Tumors Working Party

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Summary:

Extragonadal germ cell tumors are classified according to the staging system of the International Germ Cell Cancer Collaborative Group (IGCCCG). The 5-year overall and disease-free survival rates for poor prognosis patients are 41 and 48%, respectively after standard-dose chemotherapy. We report the experience of the EBMT Solid Tumours Working Party (STWP) with first-line HDCT with hematopoietic progenitor cell support (HPCS) in patients with poor prognosis extragonadal nonseminomatous germ cell tumor (NSGCT). Between 1990 and 2001, 22 extragonadal NSGCT patients (21 M, 1 F), median age 30 years (range 17–52) were treated with first-line HDCT with HPCS. Primary site was mediastinum in 11 patients, retroperitoneum in 10, and unknown in one. The Carbopec regimen, consisting of high doses of carboplatin, etoposide, and cyclophosphamide, was used in most cases (12 patients). No treatment-related deaths occurred. No patient developed myelodysplasia or a secondary leukemia. In total, 17 of 22 patients (77%) achieved complete remission. At a median follow-up of 50 months (range 26–132), 15 patients (68%) are alive disease-free. The survival rates of patients with poor prognosis extragonadal NSGCT treated with first-line HDCT in the EBMT STWP experience appear higher than that expected according to the IGCCCG classification.

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Extragonadal germ cell tumors represent a small subset of 2–5% of all germ cell malignancies.[1] In adult patients, they arise in the midline of the body, and most commonly are found in the mediastinum and retroperitoneum.[2] Extragonadal germ cell malignancies are classified according to the staging system of the International Germ Cell Cancer Collaborative Group (IGCCCG), and are treated with the same chemotherapeutic regimens as patients with a testicular primary site.[3–5] The poor prognosis group includes nonseminomatous germ cell tumors (NSGCTs) with any of the following characteristics: mediastinal primary site or nonpulmonary visceral metastases or very high serum tumor marker levels: beta-human chorionic gonadotropin (bHCG) $>50\,000$ IU/l or alpha-fetoprotein (AFP) $>10\,000$ ng/ml or lactate dehydrogenase (LDH) $>10\times$ upper limit of the normal. The 5-year overall and disease-free survival rates for poor prognosis NSGCT patients are 41 and 48%, respectively, after standard-dose chemotherapy. Results of a recent International analysis showed that, after standard-dose platinum-based primary chemotherapy with or without secondary surgery, 141 patients (49%) with mediastinal NSGCT (median follow-up, 19 months) and 144 patients (63%) with retroperitoneal NSGCT (median follow-up, 29 months) were alive ($P<0.0006$).[6]

High-dose chemotherapy (HDCT) with hematopoietic progenitor cell support (HPCS) was initially studied in relapsed or refractory GCT.[7–9] In the last few years, several attempts have been made to improve the outcome of patients with poor prognosis NSGCT, including the use of HDCT with HPCS as first-line treatment.[10–12]

To better characterize this issue, we reviewed the large database of the patients registered with the European Group for Blood and Marrow Transplantation (EBMT) with first-line HDCT with HPCS in patients with poor prognosis GCT, reclassified according to IGCCCG classification, and analyzed long-term survival data.

Patients and methods

From December 1987 to December 1999, a total of 160 patients with a diagnosis of extragonadal germ cell tumor were registered with the EBMT. NSGCTs were classified as embryonal carcinoma, teratocarcinoma, choriocarcinoma or mixed GCTs, mature or immature teratoma, and yolk sac tumor according to the World Health Organization classification. Patients with histologically undifferentiated tumors with markedly elevated serum markers, who were treated according to germ cell tumor protocols, are included in this report. We reviewed the registration details of these patients. The reporting physicians were contacted and asked to provide further information on the primary tumor site and extent of disease, histology, tumor markers, induction treatment, HDCT schedules and toxicities, further treatments, follow-up, and data on possible secondary neoplasm. For data collection, a standardized questionnaire was sent to each center. All patient data were obtained in an anonymous manner. Of 160 registered cases, 120 (75%) questionnaires were returned. In patients who achieve only a partial remission with positive serum tumor marker after induction therapy, some authors consider HDCT as initial salvage, rather than late intensification of initial therapy.[13] In accordance with these authors, we analyzed patients receiving HDCT after achieving complete remission or partial remission with negative tumor marker after induction therapy. Of all these patients, 23 were treated with HDCT as first-line setting. One case was not classifiable as poor prognosis according to IGCCCG classification. Overall, we analyzed 22 cases of poor prognosis extragonadal NSGCTs treated with HDCT as first-line treatment. As this is a report of registry data, there are cases where information is incomplete as indicated in the tables.

Patient characteristics

Details of the 22 patients with extragonadal NSGCT treated with HDCT as first-line treatment are listed in Table 1. The median age was 30 years (range 17–52). In all, 21 patients were males and one was female. A total of 11 patients had primary mediastinal NSGCT, 10 primary retroperitoneal location, and in one case primary site was unknown. All these patients were retrospectively classified with poor prognosis according to the IGCCCG classification.

Treatment

The conventional-dose induction regimens prior to HDCT were cisplatin, etoposide, bleomycin (PEB) in 10 patients, etoposide, ifosfamide, cisplatin (VIP) in seven, and the combination of cisplatin, etoposide, ifosfamide, vinblastine, and bleomycin in one. The median number of induction treatment cycles was 4 (range 2–6). Four patients were treated with only one course of mobilizing chemotherapy that was followed by multiple courses of HDCT. Table 2 summarizes induction/mobilizing chemotherapy regimens and response. Totally, 35 courses of HDCT were administered. In all, 15 patients underwent one course of HDCT, two received two courses, four received three courses, while in one case four courses were given. Patients were treated with one to four courses of HDCT based on HDCT approach in each center in the time that the treatment was administered. Totally, 25 courses were supported by peripheral blood progenitor cells (PBPCs), nine by autologous bone marrow transplantation, and one by both of them. Mobilizing courses for PBSC collection were in most

Table 1 Patient characteristics

Characteristics	*No. of patients*
Total patients	22
Male/female	21/1
Median age, years (range)	30 (17–52)
Histology	
Yolk sac tumor	5
Embryonal carcinoma	3
Choriocarcinoma	3
Undifferentiated germ cell tumor	3
Immature teratoma	2
Other germ cell tumor histology	9
Location of primary tumor	
Mediastinum	11
Retroperitoneum	10
Unknown	1
Sites of disease	
Mediastinum	14
Retroperitoneum	10
Lung	10
Liver	4
Other	5
Elevated serum tumor marker	
Alpha-fetoprotein	11
Median, ng/ml (range)	590 (1–216 000)
Human chorionic gonadotropin	11
Median, IU/l (range)	449 (0–600 000)
Lactate dehydrogenase	7
Median, IU/l (range)	679 (160–2307)

Table 2 Induction chemotherapy regimen and response

	No. of patients	*%*
Induction chemotherapy		
Cisplatin/etoposide/bleomycin (PEB)[a]	10	45
Cisplatin/etoposide/ifosfamide (VIP)[b]	7	32
Cisplatin/etoposide/ifosfamide/vinblastine/ bleomycin[a]	1	5
One mobilizing course with epirubicin	2	9
One mobilizing course with VIP	2	9
Response		
Complete remission	6	27
Partial remission, negative marker	12	55
Not evaluated after single mobilizing course	4	18

[a]In one case, followed by one mobilizing course with cyclophosphamide 7 g/m^2.
[b]In one case, followed by one mobilizing course with cisplatin/etoposide/ cyclophosphamide.

of cases included into the induction regimen, but in other cases one mobilizing course was given (Table 2).

Definitions

Tumor response was classified as follows: complete remission (CR) was defined as a complete disappearance of all clinical, radiological, and biochemical evidence of disease, with normalization of the tumor markers, bHCG and/or AFP and/or LDH, for at least a 1-month duration. A partial response was defined as a decrease in 50% or more of the sum of the products of perpendicular diameters of measurable disease, lasting at least for 1 month. If elevated markers were the only evidence of disease, a decrease of 90% or greater was required for a partial response (PR). In addition, reduction of the size of a tumor lesion and normalization of previously elevated tumor markers was considered a partial remission with tumor marker normalization (PR−), whereas a reduction $\geqslant 50\%$ in the sum of the perpendicular diameters of measurable disease plus a tumor marker decrease for at least 1 month, but without complete normalization, was considered a marker positive partial remission (PR+). 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 the occurrence of new lesions and/or elevation of tumor markers at repeated controls. Patients who achieved a normalization of tumor markers but an incomplete radiographic response were submitted to postchemotherapy surgery. However, in some patients who had attained serologic CR, but with persistent minor radiographic abnormalities, individual investigators had chosen to observe such patients without surgery.

Statistical analysis

Descriptive statistics are presented as the median and range. Duration of follow-up and survival in this analysis were calculated based on the date of the first day of the induction chemotherapy until the date of last contact, if the patient was still alive, or until the date of death. Probabilities of disease-free and overall survival were calculated using the Kaplan–Meier product limit estimate.[14]

Results

Toxicity

Toxicity data were fully assessable for 33 (94%) of 35 HDCT cycles delivered. No cases of treatment-related death occurred. The median time to recovery of an absolute neutrophil count $>500/\mu$l and a platelet count $>20\,000/\mu$l, respectively, was 8 days (range 4–28) and 6 days (range 2–32). The median number of transfusions of red blood cell and platelet bags was 4 (range 0–18) and 3 (range 1–17), respectively. Fever occurred in 24 courses (73%), with an overall median duration of 2 days (range 0–9). The number of HDCT courses with episodes of clinically documented infections was 9 (33%).

The following nonhematologic side effects were the most relevant: grade $\geqslant 3$ stomatitis was reported in eight courses, grade $\geqslant 3$ peripheral neurotoxicity in three, grade $\geqslant 3$ liver toxicity in one, grade $\geqslant 3$ ototoxicity in one, and cerebral edema in one. No patients developed myelodysplasia or secondary neoplasms after HDCT.

Response and long-term survival

Overall, 10 patients achieved a CR, eight patients a PR−, one PRm+, one SD, and two PD. Of eight patients achieving PR−, seven underwent excision of residual masses. In six cases radical surgery was complete and patients obtained a CR, but in one it was incomplete. Moreover, patients with SD after HDCT received radical surgery with CR. In total, 17 patients (76%) achieved a CR. With a median follow-up of 50 months (range 26–132 months), 14 patients (64%) are continuously disease-free (Figure 1). Of three patients who had disease recurrence, one achieved disease-free status with further chemotherapy. In total, 15 patients (67%) are currently alive disease-free (Figure 2).

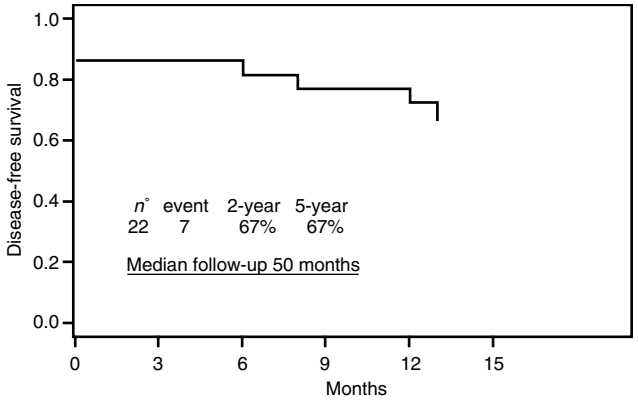


Figure 1 Disease-free survival rate of poor prognosis extragonadal germ cell tumor patients receiving first-line high-dose chemotherapy.

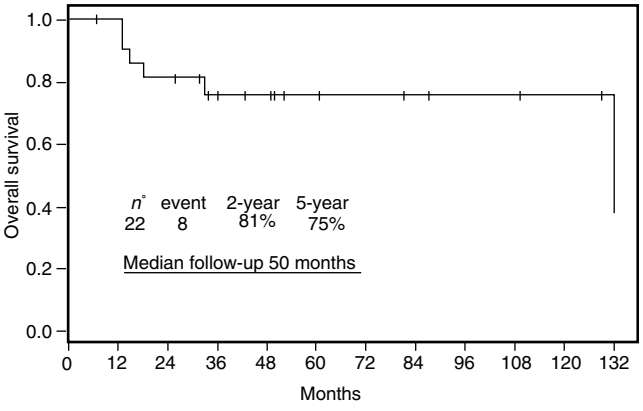


Figure 2 Overall survival rate of poor prognosis extragonadal germ cell tumor patients receiving first-line high-dose chemotherapy.

Table 3 Late-intensification high-dose chemotherapy regimen

	No. of patients	*%*
High-dose chemotherapy regimen		
Carboplatin/Etoposide/Cyclophosphamide	12	55
Carboplatin/Etoposide/Ifosfamide	5	23
Cisplatin/Etoposide/ifosfamide + paclitaxel	3	13
Other platinum-based regimen	2	9

Of 11 patients with mediastinal primary NSGCT, seven (64%) are currently disease-free. Of 10 patients with retroperitoneal primary, eight (80%) are currently disease-free. HDCT regimens are detailed in Table 3.

Discussion

HDCT with HPCS has become a therapeutic option for patients with relapsed or refractory GCT and as first-line treatment for patients with poor prognosis GCT, with more than 300 patients being treated in Europe each year.[15] Few studies with first-line HDCT in patients with poor prognosis NSGCT have been reported, and patients with extragonadal NSGCT usually represent a small percentage. The first experiences with early HDCT in poor prognosis GCTs showed significantly improved overall and disease-free survival for patients treated with HDCT compared with prior studies, based on standard-dose chemotherapy.[11,16,17] However, the only randomized trial published so far, comparing HDCT as late intensification after three courses of cisplatin, vinblastine, etoposide, and bleomycin (PVeEB) with four courses of PVeEB, showed no benefit for the HDCT arm. However, only 114 patients were randomized, PVeEB cannot be considered a standard treatment, and the dose intensity in the HDCT arm was low.[18] Instead, the results of a matched-pair analysis indicated that first-line HDCT may induce a statistically significant improvement of the 2-year disease-free and overall survival as compared with standard chemotherapy.[19]

Recently, one large prospective study has investigated the use of first-line sequential HDCT with HPCS for poor prognosis GCTs. Patients received one course of cisplatin, etoposide, and ifosfamide (VIP), followed by three to four courses of high-dose VIP with HPCS. The 5-year disease-free and disease-specific survival rates for all patients were 68 and 73%, respectively. Patients with a primary retroperitoneal NSGCT achieved a 5-year disease-specific survival of 76%, while patients with a mediastinal primary reached 67%.[20]

In the EBMT experience with chemotherapeutic regimens including one to four courses of early HDCT after induction chemotherapy, 17 patients (76%) achieved a CR, and 15 (67%) are currently disease-free at a median follow-up of 50 months (range 26–132). No toxic death occurred and no patient developed myelodysplasia or secondary leukemia after HDCT. Of 11 patients with mediastinal primary NSGCT, seven (64%) are currently disease-free. Of 10 patients with retroperitoneal primary, eight (80%) are currently disease-free. The results of the EBMT experience are comparable to those reported in other studies with early HDCT in GCT patients with poor prognosis disease, as defined by the IGCCCG criteria, and confirmed the favorable long-term outcome of these patients with extragonadal NSGCT.

Three phase III randomized studies are ongoing in patients with poor prognosis NSGCT, including patients with extragonadal NSGCT. A US Intergroup phase III randomized trial compares four courses of PEB with two courses of PEB, followed by two courses of HDCT with HPCS. In a phase III randomized study, the European Organization for Research and Treatment of Cancer (EORTC) is comparing four courses of PEB with one course of standard-dose VIP, followed by three courses of high-dose VIP and HPCS. An Italian phase III randomized study is comparing four courses of PEB with two courses of PEB followed by high-dose sequential consisting of one course of high-dose cyclophosphamide, two cycles of a super-PEB (containing high-dose etoposide), and one final course of high-dose carboplatin.

Recently, a prognostic score has been identified in extragonadal GCTs, which in part differs from gonadal GCTs.[21] The proposed model might help to better define risk-adapted treatment strategies.

In the EBMT experience, early HDCT induced impressive long-term disease-free survival in poor prognosis extragonadal NSGCT patients, particularly in patients with retroperitoneal primary site. Final results of the three ongoing phase III randomized trials are needed to define the role of HDCT as a part of initial management of poor prognosis extragonadal GCT patients. Validated prognostic models specific for extragonadal GCTs could help to tailor the HDCT option.

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Appendix

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