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Second-line high-dose chemotherapy in patients with mediastinal and retroperitoneal primary non-seminomatous germ cell tumors: the EBMT experience

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Background: Results of second-line chemotherapy in patients with extragonadal non-seminomatous germ cell tumor (NSGCT) appear inferior to results in testicular NSGCT. Patients with retroperitoneal NSGCT achieve a comparable long-term survival rate of 30%, but the salvage rates of patients with mediastinal primary are less than 10%. We conducted a retrospective analysis on patients with mediastinal and retroperitoneal NSGCT treated with second-line high-dose chemotherapy (HDCT) registered with the European Group for Blood and Marrow Transplantation (EBMT).

Patients and methods: Between 1987 and 1999, 59 registered patients with retroperitoneal ($n = 37$) and mediastinal ($n = 22$) primary NSGCT, median age 28 years (range 18–60), were treated with second-line HDCT. All had received cisplatin-containing chemotherapy as first-line treatment.

Results: Toxic death occurred in three cases (5%). With a median follow-up of 58 months (range 14–114), 18/59 patients (30%) continue to be disease-free. Of three patients who had a disease recurrence after HDCT, one patient achieved a disease-free status with further chemotherapy and surgery. In total, 19 patients (32%) are currently disease-free. Sixteen of 37 patients (43%) with retroperitoneal NSGCT, and three of 22 patients (14%) with mediastinal NSGCT are currently alive and disease-free.

Conclusions: Second-line HDCT might represent a possible option for patients with retroperitoneal primary NSGCT. New salvage strategies are needed for patients with mediastinal NSGCT.

Key words: EBMT, extragonadal, high-dose chemotherapy, non-seminomatous germ cell tumor, second-line chemotherapy

Introduction

Germ cell malignancies arising from mediastinum and retroperitoneum represent nearly 2% to 5% of all germ cell malignancies in adults [1]. Other extremely rare extragonadal primary sites are the central nervous system (pineal and/or pituitary region), liver and lung [2]. Extragonadal and testicular germ cell tumors differ in some biological, histological and clinical features. In particular, mediastinal non-seminomatous germ cell tumor (NSGCT) is associated with Klinefelter's syndrome and with hematological malignancies, sarcomatous elements are found more frequently in its pathological specimens, and a poor prognosis is recognized in these patients [3–6]. Patients with extragonadal NSGCT are included in the same international staging classification and are treated with the same chemotherapeutic regimens as patients with testicular NSGCT [6]. Recently, for the first time, a retrospective study has focused on second-line chemotherapy in patients with primary mediastinal and retroperitoneal NSGCT [7]. These patients appeared to have a survival rate inferior to patients with testicular NSGCT. Mediastinal primary site and absolute refractory disease to first-line cisplatin-based chemotherapy have been identified as independent negative prognostic factors.

Fossa et al. [8] defined prognostic factors in patients with NSGCT progressing or relapsing after primary platinum-based

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chemotherapy, identifying a poor prognosis group with no patient surviving after 3 years. This group included patients with all the following three prognostic factors: progression-free interval after first-line chemotherapy of less than 2 years; no complete remission to induction therapy; and high markers at relapse [α-fetoprotein >100 ng/ml or β-human chorionic gonadotropin (HCG) >100 IU/l]. These results have not been validated either in extragonadal NSGCT patients or in patients receiving high-dose chemotherapy (HDCT) as salvage therapy.

Beyer et al. [9] validated a prognostic index for patients with germ cell tumor receiving HDCT as salvage treatment. One point each was given for progressive disease before HDCT and mediastinal primary NSGCT or refractory disease. Two points were given for β-HCG levels >1000 IU/l before HDCT or absolute refractory disease. Patients with a cumulative score ≥3 were placed in the poor risk category.

To characterize better the role of HDCT in patients with extragonadal NSGCT, the large database of the patients registered with the European Group for Blood and Marrow Transplantation (EBMT) was reviewed. This report describes the EBMT experience of second-line HDCT in patients with mediastinal and retroperitoneal primary NSGCT.

Patients and methods

Data collection

From December 1987 to December 1999, a total of 160 patients with a diagnosis of extragonadal germ cell tumor were registered with the EBMT. The diagnosis of extragonadal germ cell tumor was defined as a germ cell neoplasm arising in the retroperitoneum, mediastinum or other location, without demonstrable gonadal (testicular/ovarian) abnormalities as assessed by ultrasonography. Gonadal biopsies were performed in patients with abnormalities on gonadal ultrasonography. NSGCTs were classified as embryonal carcinoma, choriocarcinoma mature or immature teratoma, yolk sac tumor and mixed germ cell tumors, 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 primary tumor site and extent of disease, histology, tumor markers, initial treatment, second-line chemotherapy, HDCT drugs and toxicities, follow-up and data on possible secondary neoplasms. 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 questionnaires were returned (redemption rate, 75%). Of all these patients, 23 were treated with HDCT as late-intensification of first-line therapy, nine were treated with third-, forth- or fifth-line HDCT, four were unknown primary site, two were pure seminoma and 23 children had been removed from the present analysis. Overall, we analyzed 59 cases of primary mediastinal and retroperitoneal NSGCTs treated with second-line HDCT from 29 centers in Europe. 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 59 patients with extragonadal NSGCT relapsing after or during primary cisplatin-based chemotherapy are listed in Table 1. The median age was 28 years (range 18–60). Fifty-five patients were male and four were female. Thirty-seven patients (63%) had primary retroperitoneal and 22 (37%) had primary mediastinal NSGCT. The majority ($n = 37$, 63%) of these patients received cisplatin, etoposide and bleomycin (PEB) as first-line chemotherapy. Table 2 summarizes first-line chemotherapy regimens and response.

Table 1. Characteristics of patients receiving second-line HDCT according to primary tumor site

	Mediastinum	Retroperitoneum	Total
No. of patients	22	37	59
Male/female	21/1	34/3	55/4
Age (years)			
Median	28.5	28	28
Range	18–55	19–60	18–60
Histology			
Embryonal carcinoma	7	8	15
Choriocarcinoma	1	6	7
Immature teratoma	3	3	6
Yolk sac tumor	1	3	4
Mixed	9	13	22
Unknown	0	5	5
Sites of disease			
Lung	6	16	22
Retroperitoneum	0	20	20
Mediastinum	15	4	19
Liver	4	10	14
Bone	4	0	4
Brain	1	2	3
Others	4	2	6
Unknown	3	11	14
Elevated serum tumor marker			
α-fetoprotein >100 ng/ml 5	5	3	8
β-HCG >100 IU/l	1	6	7

HDCT, high-dose chemotherapy; β-HCG, β-human chorionic gonadotropin.

Salvage treatment

All patients received salvage HDCT as second-line treatment. The salvage HDCT regimens for extragonadal NSGCT patients were adapted based on the chemotherapeutic regimens given as initial therapy and the salvage HDCT protocols used in each center for NSGCT, including carboplatin, etoposide and other drugs proven to be active in NSGCT. Before HDCT, 45 (74%) patients received an induction and/or mobilizing regimen, more frequently VIP (cisplatin, etoposide and ifosfamide) ($n = 24$, 41%), while 14 (24%) patients were treated with up-front HDCT. Table 3 summarizes induction and/or mobilizing regimens and response. Thirty-eight patients received one course of HDCT, 18 patients received two courses, two patients received three courses, and in one case four courses were given. The most commonly used HDCT protocols were based on high-doses of carboplatin and etoposide, with or without another high-dose chemotherapeutic agent (Table 4). Hematopoietic support consisted of peripheral blood progenitor cells in 44 courses, and autologous bone marrow transplantation in 28.

Table 2. Primary chemotherapy regimens and response according to primary tumor site

	Mediastinum ($n=22$) [n (%)]	Retroperitoneum ($n=37$) [n (%)]	Total ($n=59$) [n (%)]
First-line chemotherapy			
Cisplatin/etoposide/bleomycin	14 (64)	23 (62)	37 (63)
Cisplatin/etoposide/ifosfamide	4 (18)	5 (14)	9 (15)
Other platinum-containing regimen	4 (18)	9 (24)	13 (22)
Response			
Complete remission	10 (45)	9 (24)	19 (32)
Partial remission, negative marker	1 (5)	13 (35)	14 (24)
Partial remission, positive marker	8 (36)	13 (35)	21 (36)
Stable disease	2 (9)	1 (3)	3 (5)
Progressive disease	0	1 (3)	1 (2)
Unknown	1 (5)	0	1 (2)

Table 3. Second-line induction/mobilizing regimens and response according to primary tumor site

	Mediastinum ($n=22$) [n (%)]	Retroperitoneum ($n=37$) [n (%)]	Total ($n=59$) [n (%)]
Induction/mobilizing regimen			
Cisplatin/etoposide/ifosfamide	11 (50)	13 (35)	24 (41)
Cisplatin/ifosfamide/vinblastine	2 (9)	3 (8)	5 (8)
Other platinum-containing regimen	2 (9)	7 (19)	9 (15)
Other non platinum-containing regimen	2 (9)	5 (14)	7 (12)
No induction/mobilizing regimen	5 (23)	9 (24)	14 (24)
Response			
Complete remission	2 (9)	3 (8)	5 (8)
Partial remission, negative marker	4 (18)	11 (30)	15 (25)
Partial remission, positive marker	4 (18)	10 (27)	14 (24)
Stable disease	4 (18)	1 (3)	5 (8)
Progressive disease	1 (5)	2 (5)	3 (5)
Unknown/not assessed	2 (9)	1 (3)	3 (5)
No induction/mobilizing regimen	5 (23)	9 (24)	14 (24)

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, β-HCG and/or α-fetoprotein and/or lactate dehydrogenase, 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 for at least 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 ≥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 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 serological CR, but with persistent minor radiographic abnormalities, individual investigators had chosen to observe such patients without surgery. Those patients were formally coded as PRs if their residual abnormalities remained stable or decreased on imaging studies over a 1-year period. Toxicity was evaluated according to World Health Organization classification [10].

Table 4. Second-line HDCT regimens according to primary tumor site

	Mediastinum [n (%)]	Retroperitoneum [n (%)]	Total [n (%)]
No. of HDCT courses	31	53	84
Carboplatin–etoposide-based HDCT regimen			
Carboplatin/etoposide/cyclophosphamide	8 (26)	15 (28)	23 (26)
Carboplatin/etoposide/ifosfamide	7 (23)	11 (21)	18 (20)
Carboplatin/etoposide/thiotepa	1 (3)	4 (8)	5 (6)
Carboplatin/etoposide/paclitaxel	2 (6)	2 (4)	4 (5)
Carboplatin/etoposide	5 (16)	9 (17)	14 (17)
Other platinum-based HDCT regimen			
Cisplatin/etoposide/cyclophosphamide or ifosfamide	6 (19)	4 (8)	10 (12)
Other platinum-based regimen	2 (6)	5 (9)	7 (8)
Cyclophosphamide/thiotepa HDCT regimen	0	3 (6)	3 (4)

HDCT, high-dose chemotherapy.

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 salvage 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 [11]. The log-rank test was used for comparisons of overall survival between groups [12]. A P value of <0.05 was considered to be significant.

Results

Toxicity

Toxicity data were fully assessable for 68 (81%) of 84 HDCT cycles delivered. Treatment-related death occurred in three

patients with mediastinal NSGCT after HDCT. The cause was acute respiratory distress syndrome ($n=1$), pneumonia ($n=1$) and mediastinal hemorrhage ($n=1$). The median time to recovery to an absolute neutrophil count >500/μl and a platelet count >20 000/μl, was 9.5 days (range 0–32) and 10 days (range 0–34), respectively. The median number of transfusions of red blood cell and platelet bags was five (range 0–27) and six (range 0–35), respectively. Fever occurred in 53 (78%) patients with an overall median duration of 3 days (range 0–20). The number of HDCT courses with episodes of clinically documented infections was 28 (42%). The following non-hematological side-effects were the most relevant: grade ≥3 stomatitis was reported in 28 courses, grade ≥3 peripheral neurotoxicity in eight, grade ≥3 renal toxicity in three, grade ≥3 ototoxicity in two, veno-occlusive disease in one case, gastrointestinal hemorrhage in one and pulmonary hemorrhage in one. No patients developed myelodysplasia or secondary neoplasms after HDCT.

Response and survival

Overall, 21 (36%) patients achieved a CR. Of these patients, 16 obtained a radiological CR, the other five achieved a radiological PR– and received post-HDCT resection of residual masses without evidence of viable malignant cells. Sixteen of 37 patients (43%) with retroperitoneal primary NSGCT, and five of 22 patients (23%) with mediastinal primary NSGCT achieved a CR. Results are presented in detail in Table 5. The median follow-up period for all patients was 14 months (range 1–114) and 58 months (range 14–114) for surviving patients. Eighteen of 59 patients (30%) continue to be disease-free. Of three patients who had a disease recurrence after HDCT, one underwent further chemotherapy and surgery and achieved a disease-free status. In total, 19 patients (32%) are currently disease-free (Table 5). Sixteen of 37 patients (43%) with retroperitoneal primary NSGCT, and three of 22 patients (14%) with mediastinal primary NSGCT are currently alive and disease-free. Figure 1 illustrates the outcome of patients with extragonadal NSGCT, according to the primary site. The median survival time was 28 months for patients with retroperitoneal NSGCT, and 11 months for patients with mediastinal primary. The 3-year overall survival rates were 48% and 14%, respectively.

According to the predictive score derived from the study of Fossa et al. [8], 13 patients with all three risk factors were identified with a median overall survival of 11 months (range 3–16). None of these patients achieved a disease-free status.

According to the prognostic index validated by Beyer et al. [9], the only two patients stratified into the poor risk category died of disease after 5 and 14 months, respectively.

Discussion

In this report, we have presented the results of the EBMT experience with HDCT as second-line treatment for patients with extragonadal NSGCT. To the best of our knowledge, this is the largest experience with HDCT in this setting. With a median follow-up of 58 months (range 14–114), of 59 extragonadal NSGCT patients who received second-line HDCT, 18 (30%) have been disease-free continuously. Since another patient with disease recurrence achieved a disease-free status after further chemotherapy, 19 extragonadal NSGCT patients (32%) are currently disease-free: 16/37 patients (43%) with retroperitoneal primary NSGCT, and three of 22 patients (14%) with mediastinal primary.

We analyzed our results according to the prognostic index validated by the study of Fossa et al., which identified a poor

Table 5. Second-line HDCT: response and outcome according to primary tumor site

	Mediastinum ($n=22$) [n (%)]	Retroperitoneum ($n=37$) [n (%)]	Total ($n=59$) [n (%)]
Response			
Complete remission[a]	5 (23)	16 (43)	21 (36)
Partial remission with negative marker 1	(5)	7 (19)	8 (14)
Partial remission with positive marker 3	(14)	6 (16)	9 (15)
Stable disease	4 (18)	2 (5)	6 (10)
Progressive disease	6 (27)	4 (11)	10 (17)
Treatment-related death	3 (14)	0	3 (5)
Unknown	0	2 (5)	2 (3)
Outcome			
Alive continuously disease-free	3 (14)	15 (41)	18 (30)
Alive currently disease-free[b]	0	1 (3)	1 (2)
Alive with disease	0	1 (3)	1 (2)
Dead of disease	16 (73)	20 (54)	36 (61)
Treatment-related death	3 (14)	0	3 (5)

[a]Five patients obtaining a partial remission with negative marker and receiving post-HDCT resection of residual masses without evidence of viable malignant cells were also included in this group.
[b]Patient with disease recurrence achieving a second disease-free status after further chemotherapy and surgery.
HDCT, high-dose chemotherapy.

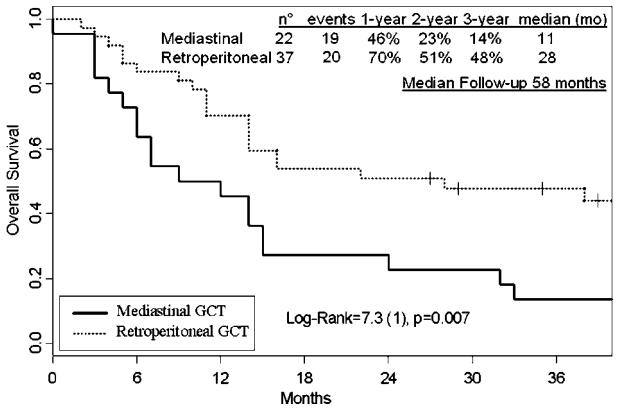

Figure 1. Overall survival for patients with mediastinal and retroperitoneal germ cell tumor (GCT).

prognosis group of NSGCT patients progressing after platinum-based first-line chemotherapy [8]. Patients with all three risk factors had a very poor prognosis and none of these patients survived beyond 16 months. Therefore, in the EBMT experience, the prognostic index also predicted outcome in patients with extragonadal NSGCT who received HDCT as salvage treatment.

In addition, we evaluated our results according to the Beyer prognostic classification for patients with germ cell tumor, treated with salvage HDCT [9]. Only two patients were stratified into the poor risk category and died of disease after 5 and 14 months, respectively. The publication in 1996 of the Beyer classification could have induced a better patient selection for salvage HDCT.

Several studies of salvage chemotherapy for patients with NSGCT included patients with extragonadal primary, but these patients usually represented a small percentage. Loehrer et al. [13] reported the largest experience with vinblastine, ifosfamide and cisplatin as second-line therapy for germ cell tumor. None of the 32 patients with non-seminomatous extragonadal tumors are disease-free compared with 30 of 100 patients with gonadal primaries. Other studies have investigated the use of HDCT in patients with relapsed NSGCT [9, 14–16]. Saxman et al. [14] presented a series of 73 extragonadal NSGCT treated with salvage chemotherapy. Only 7% of their patients achieved long-term disease-free survival. None of the 28 patients who received HDCT as initial salvage treatment ($n=8$) and as third-line treatment ($n=20$) were long-term disease-free. In the large multivariate analysis reported by Beyer et al., including 282 patients with germ cell tumors treated with salvage HDCT, mediastinal primary site and refractory disease were identified as the most important poor prognostic factors [9]. Recently, Vaena et al. [15] showed a 37% long-term survival rate in 63 patients with platinum-refractory germ cell tumors treated with early tandem HDCT, but no patients with mediastinal primary NSGCT survived disease-free at 2 years.

In the largest reported series including 142 patients with relapsed extragonadal NSGCT treated with second-line chemotherapy, patients with retroperitoneal primary NSGCT achieved a long-term survival rate of 30%, but those with mediastinal primary had salvage rates of less than 10% [7]. Both primary mediastinal location and refractoriness to cisplatin were found to be independent negative factors. In this series, 28% of patients with mediastinal primary and 41% of patients with retroperitoneal NSGCT were treated with second-line HDCT. The median survival time was 15 months for patients receiving HDCT and 11 months for patients treated with standard-dose chemotherapy. Although, the survival curves are in favor of HDCT, there was no statistically significant difference between both groups in term of median survival ($P=0.27$). However, seven of 22 (32%) patients with retroperitoneal NSGCT receiving HDCT and 11/39 (28%) who underwent conventional-dose chemotherapy were alive without disease. In total, the 3-year overall survival for the subpopulation of patients with chemosensitive retroperitoneal primary NSGCT was 26%, while for patients with chemosensitive mediastinal primary it was 11%.

In the EBMT experience, all extragonadal NSGCT patients, but one, were chemosensitive (Table 2). The 3-year overall survival for patients with retroperitoneal primary NSGCT was 48%, while for patients with mediastinal primary it was 14%, as shown in Figure 1. Results in the subset of chemosensitive retroperitoneal NSGCT might appear in favor of the use of second-line HDCT, while HDCT has no substantial impact on the outcome of patients with mediastinal primary site. However, this hypothesis must be considered with caution because a systematic bias based on patient selection for HDCT might have influenced these findings.

In order to clarify the exact role of HDCT in patients with chemosensitive germ cell tumors, a phase III randomized study performed by EBMT (IT-94 study) was carried out [17]. This trial compared four courses of conventional salvage chemotherapy with three courses of the same regimen followed by one single shot of HDCT. Definitive results will possibly better define the role of HDCT in the subpopulation of patients with extragonadal NSGCT, but the number of these patients, not included in the present analysis, was too limited to draw any firm conclusion.

In summary, results of the EBMT experience showed a possible role for second-line HDCT for chemosensitive patients with retroperitoneal NSGCT. Final results from larger studies could eventually better define the role of salvage HDCT for patients with extragonadal NSGCT. New strategies are needed for salvage treatment of patients with mediastinal NSGCT.

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Appendix

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