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Post-Relapse Survival in Patients With Ewing Sarcoma

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Background. Post-relapse survival (PRS) was evaluated in patients with Ewing sarcoma (EWS) enrolled in chemotherapy protocols based on the use of high-dose chemotherapy with busulfan and melfalan (HDT) as a first-line consolidation treatment in high-risk patients. ***Procedure.*** EWS patients enrolled in ISG/SSG III and IV trials who relapsed after complete remission were included in the analysis. At recurrence, chemotherapy based on high-dose ifosfamide was foreseen, and patients who responded but had not received HDT underwent consolidation therapy with HDT. ***Results.*** Data from 107 EWS patients were included in the analysis. Median time to recurrence (RFI) was 18 months, and 45 (42%) patients had multiple sites of recurrence. Patients who had previously been treated with HDT had a significantly ($P = 0.02$) shorter RFI and were less likely to achieve a second complete remission (CR2). CR2 status was achieved by 42 (39%) patients. Fifty patients received high-dose IFO (20 went to consolidation HDT). The 5-year PRS was 19% (95% CI 11 to 27%). With CR2, the 5-year PRS was 48% (95% CI 31 to 64%). Without CR2, median time to death was six months (range 1–45 months). According to the multivariate analysis, patients younger than 15 years, recurrence to the lung only, and RFI longer than 24 months significantly influenced the probability of PRS. ***Conclusions.*** Age, pattern of recurrence, RFI, and response to second-line chemotherapy influence post-relapse survival in patients with recurrent Ewing sarcoma. No survival advantage was observed from chemotherapy consolidation with HDT. Pediatr Blood Cancer 2015;62:994–999.

Key words: Ewing sarcoma; metastases; chemotherapy; high-dose chemotherapy

INTRODUCTION

For Ewing sarcoma (EWS), approximately 30–40% of patients experience tumor recurrence despite intensive chemotherapy combined with local surgical treatment and/or radiotherapy [1]. The recurrence rate is even higher for patients with synchronous metastases at presentation [1]. Additionally, post-relapse survival is poor; less than 15% at five years has been reported in many studies [2–4]. Relapse-free interval (RFI), pattern of recurrence, and response to second-line chemotherapy are factors that influence the outcome of patients [2–4].

EWS is the only bone sarcoma that is currently treated with consolidation treatment with high-dose chemotherapy (HDT) and peripheral blood stem cell rescue. In high risk patients, HDT has been adopted both at the time of recurrence and in first-line treatment [5–11].

The Italian Sarcoma Group and the Scandinavian Sarcoma Group together performed prospective trials characterized by standard chemotherapy treatment followed by HDT in patients with localized (ISG/SSG-III) and metastatic (ISG/SSG-IV) EWS [9,10]. All patients with synchronous metastases who had radiographic response were candidates for HDT, whereas, in patients with localized disease, consolidation with HDT was reserved only to poor responders to induction chemotherapy.

At the time of recurrence, chemotherapy treatment based on ifosfamide was recommended. The patients who responded and had not previously received HDT underwent HDT. Pattern of recurrence, treatment, and post-relapse survival of patients enrolled in ISG/SSG III and ISG/SSG IV protocols are herein reported with emphasis on the evaluation of the systemic treatment at the time of recurrence.

METHODS

Patients enrolled in ISG/SSG-III and ISG/SSG-IV protocols that had local and/or distant recurrence after chemotherapy completion were eligible for the study [9,10]. Patients who progressed during first-line chemotherapy and those lacking information about the pattern of recurrence, type of treatment, and post- relapse survival were excluded from the analysis.

All patients had a histological diagnosis of EWS. ISG/SSG-III enrolled patients up to 40 years of age, with no evidence of metastases [9]. After induction chemotherapy with vincristine (V), doxorubicin (A), cyclophoshamide (C), actinomycin (Ac), ifosfamide (I), and etoposide (E), poor responders (PR) received three cycles of VAC-IE and a mobilizing cycle with C, E, and HDT with busulfan and melphalan with stem cell support. Good responders (GR) received nine cycles of VACAc-IE regimen. ISG/SSG-IV enrolled patients up to 40 years of age with synchronous metastases in the lung only, pleural involvement/effusion or single bone metastasis [10]. Treatment consisted of an intensive five-drug combination chemotherapy (V,A,I,C,E), surgery and/or radiotherapy as local treatment, and consolidation treatment with HDT and total-lung irradiation.

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After chemotherapy completion, patients were followed at 3-month intervals for the first three years, every four months during the 4th and 5th year and after that every six months. Chest X-rays or chest computed tomography (CT), X-rays or magnetic resonance imaging (MR) or CT of the affected bone were performed at each follow-up visit. Bone scan and plain X-rays were taken in case of clinical suspicion (pain and/or swelling) of bone metastases (CT or MR were used when bone scan or plain X-rays showed a radiographic pattern of possible bone metastases). Data for the present analysis were retrieved from ISG/SSG-III and ISG/SSG-IV master files. Additional information was obtained from the review of clinical charts.

At the time of recurrence, patients were candidates for chemotherapy treatment based on high-dose ifosfamide (3 g/m^2/day plus mesna over a 5-day continuous infusion). When tumor response was complete or partial after two cycles of high-dose IFO, patients who had not received HDT in first-line underwent peripheral blood stem cell (PBSC) harvest after mobilizing cycle with cyclophosphamide (4 g/m^2) and etoposide (150 mg/m^2/day for four days) + G-CSF. HDT (busulfan 4 mg/kg × 4 days orally or 3.2 mg/kg × 4 days intravenously and melphalan 140 mg/m^2) with PBSC rescue was subsequently administered. Patients with tumor response who had previously received HDT after two cycles of high-dose IFO received another two cycles of high-dose IFO. Local treatment for recurrence was planned according to the extent and site of metastases and was usually preceded by chemotherapy. When lung metastases were resectable and the relapse-free interval was longer than two years, nodule surgery followed by total lung radiotherapy (12–15 Gy) was recommended.

STATISTICS

Relapse-free interval (RFI) was defined as the time from initial diagnosis to the first recurrence (local and/or distant). Post-relapse survival (PRS) was defined as the time from detection of recurrence and death for any cause. Second complete remission (CR2) was defined as the status of patients who had disease remission in all metastatic sites treated with curative intent by radiotherapy and/or surgery.

A two-sample *t*-test and contingency table analysis was used when appropriate. For multiple groups, comparison analysis of variance (ANOVA) was performed.

Statistical analyses of PRS were performed using the Kaplan-Meier method for calculating survival curves and a 95% confidence interval (CI). PRS differences among groups were analyzed using the log-rank test. Multivariate analysis of relative risks with 95% CI was performed by Cox proportional hazards model.

RESULTS

In ISG/SSG-IV, 102 patients were enrolled, 71 completed the planned protocol treatment, and 26 had tumor recurrence [10]. Updated results of ISG/SSG-III protocol showed that of the 300 patients enrolled, 97 [32%] had a disease-related event, 10 cases while on therapy, and 87 cases after first complete remission (CR1). Overall, 113 patients had tumor recurrence after CR1. Six were excluded for missing data, and 107 were included in the present analysis. Patient characteristics are listed in Table I.

TABLE I. Patient Characteristics

Age [years]	No. [%]
Median [min–max]	19 [6–43]
Sex	
Male	67 [63]
Female	40 [37]
RFI [months]	
<12	19 [18]
12–24	49 [46]
>24	39 [36]
Recurrence pattern	
LR	11 [10]
Bone	17 [16]
Lung	34 [32]
Multiple sites	45 [42]
Protocol	
ISG/SSG-III	87 [81]
ISG/SSG-IV	20 [19]
HDT in first line	
Yes	53 [50]
No	54 [50]

RFI, Relapse-Free Interval; HDT, High-dose Chemotherapy; LR, Local Recurrence.

Time and Type of Recurrence

Median RFI was 18 months (10–115 months). RFI was 18 months (10–115 months) in ISG/SSG-III and 17 (11–51 months) in ISG/SSG-IV patients ($P = 0.30$). Nineteen (18%) patients experienced recurrence in the first year, 49 (46%) in the second year, and 39 (36%) had tumor recurrence after two years (five patients recurred after five years).

Overall, 33 (31%) patients had local recurrence (11 patients without distant metastases). The pattern of metastases was characterized by lung location in 34 (32%) patients, bone in 17 (16%), multiple site involvement in 45 (42%). Other sites of metastatic recurrence were lymph nodes in nine patients, brain metastases in three, and liver or skin metastases were in two patients. Histologically confirmed bone marrow involvement was documented in three patients. For local recurrence with no evidence of distant metastases RFI was 18 months (10–64), 26 months (10–115) with lung metastases, 20 months (11–101) with bone metastases, and 15 months (10–57) for multiple site involvement ($P = 0.05$).

Recurrence pattern and RFI did not differ between ISG/SSG-III and ISG/SSG-IV protocols [data not shown]. Patients who received HDT in first-line (ISG/SSG-IV and PR patients in ISG/SSG-III) had similar types of recurrence, but a significantly ($P = 0.02$) shorter median RFI (16 months (range10–56) vs. 20 months [range 10–115]).

Treatment After Recurrence

Figure 1 shows a diagram of post-recurrence treatment, CR2, and outcome of the study population. Treatment after recurrence was influenced by recurrence pattern, RFI, and performance status (PS) of patients. Ten patients with disseminated disease and poor PS were given palliative treatment. Surgery alone (10 patients) or surgery combined with radiotherapy (seven patients) was given to a

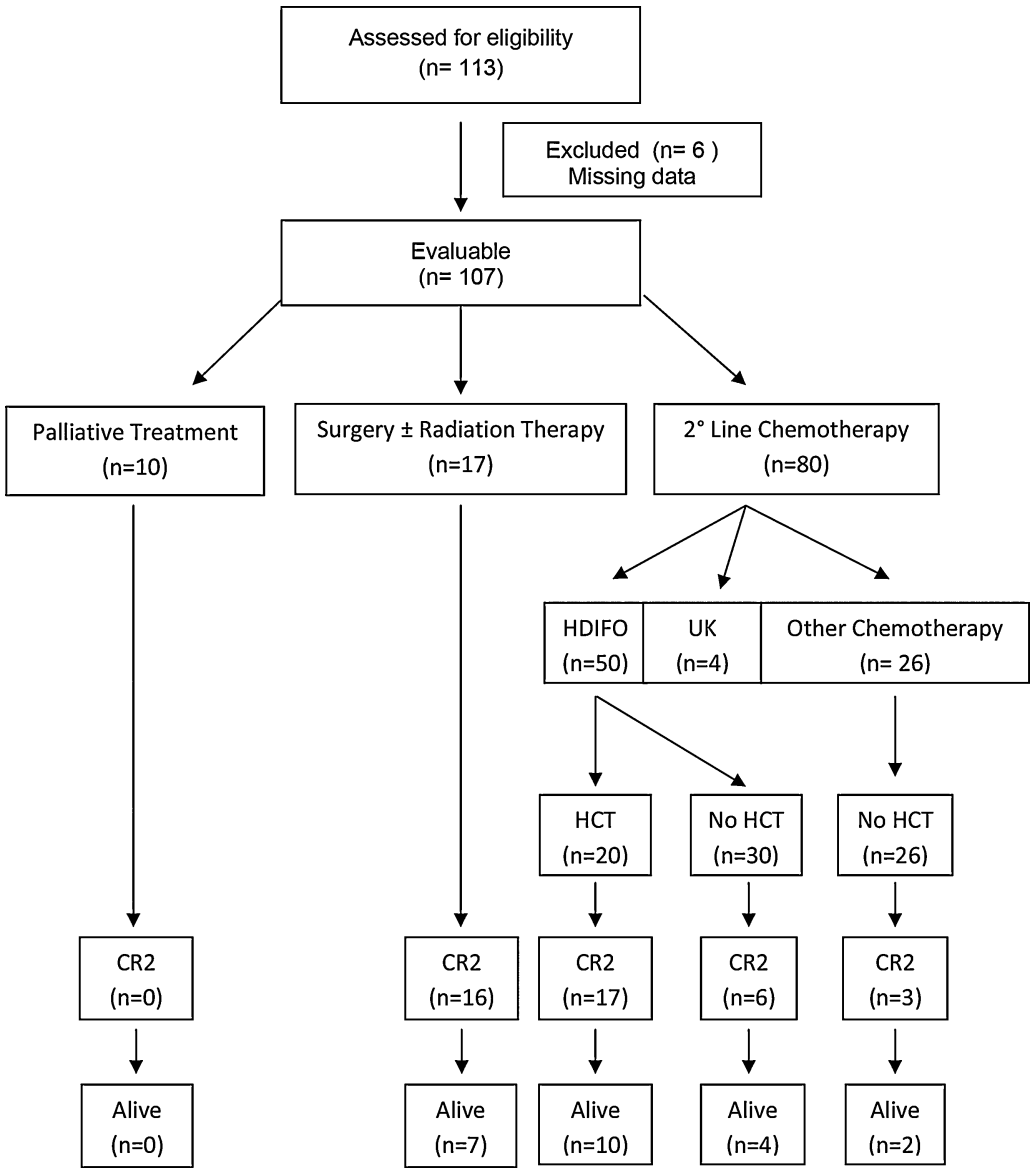

Fig. 1. Post-relapse treatment and outcome of the study population. HDIFO = High-dose Ifosfamide; UK = Chemotherapy not known; HCT = High-dose chemotherapy and peripheral blood stem cell rescue; CR2 = Second complete remission.

total of 17 patients with isolated local recurrence or lung metastases. Second-line chemotherapy was given to 80 patients. High-dose IFO was given to 50 (62.5%) patients; however, in four patients with multiple site involvement, treatment was unknown, whereas in 26 patients several antineoplastic agents were used: yclophosphamide/topotecan in five patients, Caelyx/etoposide, and vincristine/cyclophosphamide/actinomycyn-D in three patients each, trabectedin, anti-IGF1R, irinotecan in two patients each, oral etoposide and oral cyclophosphamide/weekly vinorelbine in the remaining 16 patients. Of the 50 patients who received high-dose IFO, 20 (40%) responder patients who were not pretreated with HDT in first-line went to consolidation treatment with HDT. A CR2 status was achieved in 42 (39%) patients. CR2 was more frequently attained ($P = 0.001$) in patients with only lung metastases (65%) or with local recurrence (64%) compared to patients with multiple site involvement (18%) or bone metastases (29%). A significant ($P = 0.0001$) relationship was found between RFI and CR2 (rate of CR2: RFI < 12 months 5%, RFI 12–24 months 25%, >24 months 74%). CR2 was more frequently ($P = 0.0015$) achieved in patients (55%) who received first-line standard chemotherapy compared to those pretreated with HDT (25%).

Post-Relapse Survival

The median PRS for the 107 patients was 12 months, and the 5-year PRS was 19% (95% CI 11 to 27%; Fig. 1). The 42 patients who achieved CR2 had a 5-year PRS of 48% (95% CI 31 to 64%). For the 65 patients who did not achieve CR2, the median time to death was six months (range 1–45), and the probability of PRS at two years was 3% (95% CI 0 to 8%; Fig. 1). Age, RFI, and pattern of recurrence were additional factors that influenced PRS (Table II).

TABLE II. Post Relapse Survival (PRS) Probability

	% 5-year PRS [95%CI]	*P*-value
Age [years]		0.01
6–14	28 [11–45]	
15–17	8 [0–22]	
≥ 18	19 [8–30]	
Sex		0.4
Male	23 [12–33]	
Female	12 [4–24]	
Recurrence Pattern		0.0007
LR	18 [0–41]	
Bone	23 [3–44]	
Lung	34 [17–51]	
Multiple sites	9 [0–17]	
RFI		0.0001
<12	0	
12–24	20 [9–32]	
>24	40 [23–57]	
Protocol		0.01
ISG/SSG-III	23 [14–33]	
ISG/SSG-IV	5 [0–15]	
HDT first line		0.006
Yes	9 [1–17]	
No	30 [17–44]	

Of the 50 patients who received high-dose IFO, 34 had not received HDT in first-line. Twenty patients (59%) proceeded to HDT and had a 5-year PRS of 50% (95% CI 28 to 72%). Those patients who progressed after two cycles of high-dose IFO or received only high-dose IFO because they were already treated with HDT had a 5-year PRS of 12% (95% CI 2 to 25%). The 5-year PRS was 5% (95% CI 4 to 14%) for the 30 patients who received treatments other than high-dose IFO (Fig. 1). None of the patients who had received only the best supportive care and palliative radiotherapy survived more than 12 months. Five-year post-relapse survival was 31% (95% CI 8 to 55%) in the 17 patients treated only with surgery and radiotherapy at first recurrence (Fig. 1). Of the 42 patients who achieved CR2, 27 had a further recurrence (median time to 2nd recurrence 19 months, range 2–131 months). All but one of the CR2 patients treated only with surgery and radiotherapy had a subsequent relapse. One patient who recurred with a single lung nodule with a RFI longer than 24 months was continuously free of disease eight years from recurrence. The nodule was resected and total lung irradiation was given. By multivariate analysis, younger age, recurrence to the lung only, long RFI, CR2 status were factors that significantly influenced the probability of PRS (Table III and Table IV).

Overall, seven patients died of treatment-related complications. There was one case of perioperative death in a patient who, after response to high-dose IFO, underwent thoracic surgery. Another patient died of toxicity during the second cycle with high-dose IFO due to acute central nervous system toxicity that was not properly identified by the treating physician. Two patients died of multi-organ failure after HDT. Three toxic deaths were reported in patients who underwent further chemotherapy lines in phase II studies (Fig.2).

DISCUSSION

In this article we have reported the post-relapse survival of patients with Ewing sarcoma who recurred after first-line treatment,

TABLE III. Multivariate Analysis of Clinical and Treatment Variables

Variable	RR	95%CI	*P*
Age [years]			0.0013
≤ 14	1		
15–17	3.6	1.8–7.3	
≥ 18	1.7	1–2.9	
Type of Relapse			0.055
Multiple sites	1		
Bone	0.7	0.3–1.4	
Local [only]	2.2	1–4.9	
Lung Mets	0.7	0.4–1.3	
RFI			0.0003
>24 months	1		
12-24 months	1.7	0.9–3.1	
<12 months	4.8	2.2–10.5	
Protocol			0.7
ISG/SSG IV	1		
ISG/SSG III	0.9	0.5–1.7	
HDT first line			0.4
Yes	1		
No	0.7	04v1.4	
CR2			0.0001
No	1		
Yes	0.1	0.07–0.3	

RFI, Relapse-Free Interval; HDT, High-dose Chemotherapy; CR2, Second Complete remission.

TABLE IV. Multivariate Analysis of Clinical and Treatment Variables in 80 Patients Treated With Chemotherapy

Variable	RR	95%CI	*P*
Age [years]			0.002
≤ 14	1		
15–17	5.5	2.25–13.5	
≥ 18	2.1	1–3.9	
Type of Relapse			0.3
Multiple sites	1		
Bone	0.7	0.3–1.5	
Local [only]	2.1	0.7–6.2	
Lung Mets	1.1	0.5–2.6	
RFI			0.003
>24 months	1		
12–24 months	1.7	0.9–3.4	
<12 months	4,8	1.9–12	
Protocol			0.6
ISG/SSG IV	1		
ISG/SSG III	1.3	0.6–2.7	
HDT first line			0.4
Yes	1		
No	0.8	04–1.9	
CR2			0.0001
No	1		
Yes	0.1	0.04–0.3	
Chemotherapy			0.7
Other	1		
HDIFO	0.7	0.3–1.5	
HDIFO-BuMel	0.6	0.2–2.4	

RFI, Relapse-Free Interval; HDT, High-dose Chemotherapy; LR, Local Recurrence; CR2, Second Complete remission; HDIFO, High-Dose Ifosfamide; BuMel, Busulfan and Melphalan.

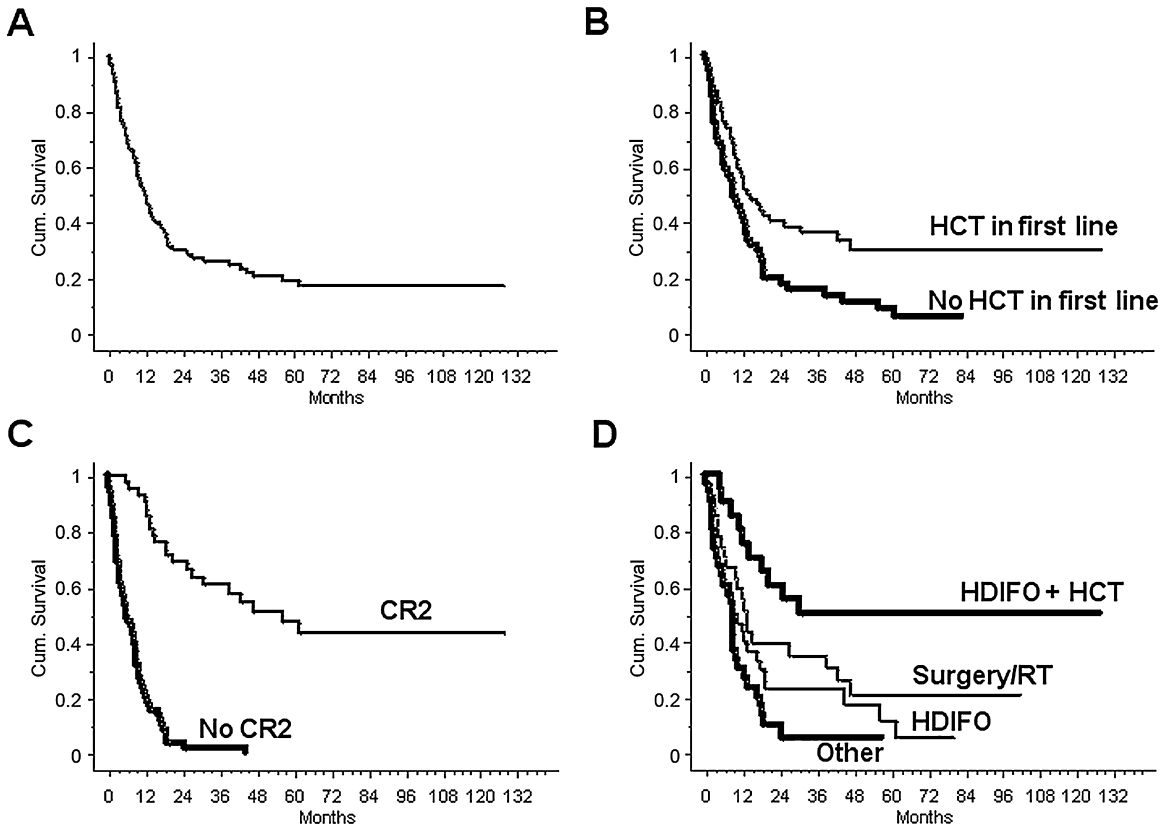

Fig. 2. Post-relapse survival curves. (A) Post-relapse survival curve; (B) Post-relapse survival curve in patients previously treated in first-line with HDT (HDT in first-line) or without HDT (no HDT in first-line). (C) Post-relapse survival curve in patients who achieved a second complete remission (CR2) or who did not achieve a second complete remission (no CR2). (D) Post-relapse survival curve in patients who responded to HDIFO and underwent HDT (HDIFO + HDT), patients who at first recurrence received only surgery ± RT (surgery/RT), patients who received only HDIFO (HDIFO) and patients who received other antineoplastic agents than HDIFO (Other). Data and statistical comparison are in the text.

including HDT. Patients who were given HDT in first-line had a significantly shorter RFI, and interestingly, only patients who received first-line standard chemotherapy showed late (over five years) relapse. All patients were non-metastatic and showed a good response to induction chemotherapy. CR2 rate was significantly lower in patients pretreated with HDT compared to that of patients who had received standard first-line chemotherapy. These data confirm the aggressive biological behavior that characterizes high risk EWS patients (localized patients with poor response to induction chemotherapy and patients with metastatic disease at presentation).

Achievement of a CR2 was the main factor influencing PRS. Patients who did not reach a CR2 had a median PRS of six months, with no patient survival 12 months after recurrence. To allow for effective treatment and hopefully a greater probability of survival by detecting recurrences early, the follow-up program in both ISG/SSG-III and ISG/SSG-IV studies was very accurate and frequent. Unfortunately, approximately 40% of patients had multiple site recurrences or recurrence in a site that did not allow a second complete remission. These conditions were mostly observed in patients pretreated with HDT.

We cannot exclude that this type of follow-up may have improved survival probability, it was however certainly associated with a relatively high rate of CR2. CR2 rate published in a previous paper in 2003 was 13% and the 5-year PRS was 14%, in the present analysis the rate of CR2 was 42% and the 5-year PRS was 19% [3].

In the present cohort, at first recurrence, some patients with isolated local recurrences or resectable lung metastases and a RFI longer than 24 months achieved CR2 with surgery and/or radiotherapy without chemotherapy. All but one patient had a subsequent recurrence. These data underline how metachronous metastases in Ewing sarcoma have a different behavior compared to osteosarcoma, for which the possibility of a cure for patients with metachronous lung metastases with surgery alone is well known [12,13]. However, the fact that one patient is continuously disease-free after recurrence confirms that there are selected patients with metastatic EWS who do not require the addition of chemotherapy [14].

As previously reported, our study also confirms that RFI is an important factor influencing PRS [2–6,15]. Patients with a positive response to first-line therapy have a median time to recurrence longer than PR patients. The type of recurrence was another factor that influenced PRS, which was better in those patients with only lung metastases. This result is similar to that of the CESS study and to a previous Rizzoli Institute study, which reported lung location of metachronous metastases as a positive prognostic factor for survival [2,3]. On the contrary, in the COG study, lung location of metastases was not reported as a positive prognostic factor [4].

Another factor that influenced post-relapse survival was age. In patients with non-metastatic EWS, it is well known that children have a better prognosis compared to other age groups [1,16]. This was not reported in previous studies on PRS, whereas in the present work we observed that an age-related probability of survival was also maintained at the time of recurrence [3,4].

Overall, our data confirm that the PRS in EWS patients is still dismal, and many patients recur with widespread disease that is not amenable to present clinical strategies. However, the results from this study show a sub-group of patients who benefitted from intensive treatment at the time of recurrence.

Most patients who received chemotherapy with a curative intent at the time of recurrence were treated with high-dose ifosfamide. A high percentage of these patients had tumor response and consolidation treatment with HDT with a 5-year PRS of 50%.

Data supporting a treatment strategy including HDT in patients with recurrent EWS have been previously reported by Barker and McTiernan and more recently by Rasper [5,6,17]. In the present study, patients who underwent HDT after recurrence were a selected group who had a good response to chemotherapy and achieved a CR2. The multivariate analysis performed clearly showed the importance of achieving a CR2 and did not confirm the statistical significance of consolidation with HDT in patients with recurrent EWS.

Overall, our data confirm the dismal prognosis of recurrent Ewing sarcoma. The main factors predictive of post-relapse survival are response to second-line chemotherapy and the possibility of achieving a second complete remission. In our series, consolidation of response with high-dose chemotherapy was not an independent variable influencing post-relapse survival.

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