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*ORIGINAL ARTICLE*

# Comparison of the treatment results after conventional and myeloablative chemotherapy in patients with poor prognosis Ewing's sarcoma family tumors - single center experience

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## Summary

***Purpose:*** *To compare the survival of patients with poor-prognosis Ewing's sarcoma family tumors (EFT) after conventional and myeloablative chemotherapy treated at our hospital in a period of 25 years.*

***Methods:*** *Fifty-seven patients were treated between 1985 and 2010. The patients were separated into 3 groups. Group A included patients (n=20) treated with conventional chemotherapy between 1985 and 1997. Group B patients (n=22) were treated with conventional chemotherapy protocols between 1997 and 2010; and group C patients (n=15) were treated in the same period of time with conventional chemotherapy and subsequent myeloablative chemotherapy with hematopoietic stem cell transplantation (HSCT).*

***Results:*** *In group A patients the 5-year overall survival (OS) was 25% and the disease-free survival (DFS) 15%; in group B patients they were 27.27% and 18.8% (p=0.31) and in group C patients 33.3% and 20% (p=0.58), respectively.*

***Conclusion:*** *More intensive chemotherapy, including myeloablative chemotherapy plus HSCT, is a curative option for patients with poor-prognosis EFT, but the survival still remains unsatisfactory.*

**Key words:** autologous transplantation, Ewing's family tumors, intensive chemotherapy, metastases, myeloablative chemotherapy, relapsed tumors

## Introduction

EFT, which includes classic Ewing's sarcoma, Askin tumor and peripheral primitive neuroectodermal tumors (PNETs), constitutes a very aggressive form of childhood cancer, being the second most common primary bone tumor in this age group [1]. Twenty-five percent of the patients have detectable metastases at diagnosis. The most common metastatic sites are the lung (50%), followed by bone (25%) and bone marrow (20%) [2].

Newer molecular biology studies have shown that all Ewing's sarcomas and PNETs share a common gene rearrangement involving genes on chromosome 22. In most cases, a reciprocal translocation t (11;22) (q24;q12) is found, but t (21;22)(q22;q12) and others may also be found. Identification of the characteristic chromosomal aberrations and the resulting EWS-FL11 gene fusion has a considerable effect on diagnosis and may affect the treatment to be given [3,4].

Despite the progress in the research of these neoplasms, there is currently no internationally recognized risk classification for Ewing's sarcoma patients. In the Children's Oncology Group studies in North America, 3 risk groups are established for patients with localized tumors, with lung metastases only, and patients with multiple or other metastases. The EuroEWING-99 study has a more complex scheme using metastatic status (none, lung and others), initial tumor size (< and > 200 ml), the subsequent resectability and histological response to initial chemotherapy to assign patients to treatment [1]. Patients with poor prognosis are those with bulky or metastatic disease at diagnosis and after relapse.

Before the introduction of chemotherapy, only 10% of patients with Ewing's sarcoma survived longer than 2 years [5]. After a dramatic treatment progress

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in the last 30 years, cure rates up to 75% and more can be achieved in localized tumors [1]. Unfortunately, the outcome of patients with metastatic disease at presentation remains poor with 5-year event-free survival of only 25% [6]. The chance for 5-year survival for patients with recurrent diseases is even worse - only 13% [7,8].

At present the therapy of EFT is multimodal and incorporate surgery, chemotherapy and/or radiation therapy [9]. Chemotherapy for Ewing's sarcoma began in the 1960s, with single-agent therapy including cyclophosphamide, dactinomycin, doxorubicin, vincristine, or carmustine, followed by single-arm multiagent adjuvant chemotherapy trials using vincristine-actinomycin-cyclophosphamide (VAC) or VAC plus doxorubicin (VACA) [5,10]. Intensification of therapy (both dose and timing) is critical to disease response. A high initial response rate and prolongation of progression-free interval (PFI) were documented with the addition of etoposide and ifosfamide to the conventional chemotherapy regimens in 1990s, especially for patients with localized tumors [11]. There has not been similar progress in the treatment of patients with metastases, even with anticancer drugs doses increased by 25-50% [1,11]. High doses severely increased acute toxicity and the incidence of secondary leukemia and myelodysplasia [6]. Patients with metastases outside the lungs at diagnosis seldom survive, and this has led to several studies using megatherapy (myeloablative chemotherapy with or without total body irradiation [TBI] and rescue with autologous bone marrow or peripheral blood stem cells transplantation), which has overcome dose-limiting toxicity and allowed further dose escalation [11,12]. A variety of myeloablative regimens followed by HSCT for patients with metastatic disease have been used but the role of this treatment remains controversial [1,9].

Very few patients with relapsed EFT achieve a second remission and are eligible for megatherapy, but the outcome remains uncertain [1].

The newly diagnosed EFT patients in Bulgaria are 4-6 annually, which corresponds to a frequency of 2-3/1,000,000 children and young adults elsewhere. Systemic chemotherapy was started between 1980 and 1985. Before the initiation of autologous transplantation in Bulgaria in 1997, about 75% of all patients with Ewing's sarcoma were treated at our hospital. Since then more than 90% of these patients are referred to our centre.

The purpose of this retrospective analysis was to compare the outcome of poor-prognosis EFT patients (with bulky initial tumor volume over 200 ml and metastatic disease at diagnosis; and after early relapse, before 2 years after diagnosis), treated at our hospital with conventional chemotherapy between 1985 and 1997 and 1997-2009, and with high-dose chemotherapy followed by autologous HSCT between 1997 and 2009.

## Methods

### *Patient characteristics*

Fifty-seven patients with poor prognosis EFT (bulky or metastatic disease at diagnosis; and after early relapse) were treated at our hospital between 1985 and 2010. Fifty-one patients had classic Ewing's sarcoma and 6 PNETs. Patient and disease characteristics are displayed in Table 1.

**Table 1.** Patient and disease characteristics

| *Characteristics* | *Number of patients (%)* |
|---|---|
| Age, years | |
| Median (range) | 12.8 (3-30) |
| Gender | |
| Group A | 10 M (50), 10 F (50) |
| Group B | 11 M (50), 11 F (50) |
| Group C | 10 M (50), 5 F (50) |
| Primary tumor localization | |
| Long bones | |
| Group A | 14 (70) |
| Group B | 7 (32) |
| Group C | 6 (40) |
| Central axis bones | |
| Group A | 6 (30) |
| Group B | 15 (68) |
| Group C | 9 (60) |
| Disease stage | |
| III (bulky disease) | |
| Group A | 9 (45) |
| Group B | 8 (36) |
| Group C | 4 (21) |
| V (metastatic disease) | |
| Group A | 7 (35) |
| Group B | 10 (45) |
| Group C | 6 (33) |
| Relapse | |
| Group A | 4 (20) |
| Group B | 4 (18) |
| Group C | 5 (33) |
| Indications for high-dose chemotherapy | |
| Sensitive relapse | 7 (41) |
| Bulky or metastatic disease | 8 (59) |
| Disease status before transplantation | |
| Complete remission | 5 (33) |
| Partial remission | 3 (20) |
| Progression | 4 (27) |
| Stable disease | 3 (20) |
| Karnovsky/Lansky performance score pretransplant | |
| ≤90 | 4 (21) |
| ≥90 | 11 (79) |

M: male, F: female

Diagnosis, histological response to first-line chemotherapy and relapses had been documented by morphology and immunohistochemistry, without molecular studies. Stage was defined according to EuroEWING-99 study criteria (initial tumor volume and evidence of metastatic disease) (Table 1). Patients with metastatic disease were those with metastases or multiple tumor localizations at diagnosis.

*Chemotherapy*

Patients were separated into 3 groups according to the chemotherapy modalities administered. Group A (20 patients) included all patients treated with conventional chemotherapy between 1985 and 1997. Group B (22 patients) included patients treated between 1997 and 2010 with conventional chemotherapy protocols containing ifosfamide and etoposide; and group C (15 patients) consisted of patients treated in the same time period with conventional chemotherapy and subsequent myeloablative chemotherapy and autologous stem cell transplantation. Female patients were 25 and males 32 with median age 12.8 years (range 3-30). Patients treated between 1985 and 1997 received VACA and VAIA. VACA consisted of vincristine 1.5 mg/m$^2$ i.v. d 1+21, doxorubicin 20 mg/m$^2$ i.v. d 1-3, cyclophosphamide 1200 mg/m$^2$ i.v. d 17-21, dactinomycin 0.5 mg/m$^2$ i.v. d 21-23, repeated after a therapy-free interval of 3 weeks for a total of 6 cycles. VAIA included vincristine 1.5 mg/m$^2$ i.v. d 1+21, doxorubicin 20 mg/m$^2$ i.v. d 1-3, ifosfamide 2,000 mg/m$^2$ i.v. d 1-3 plus mesna, dactinomycin 0.5 mg/m$^2$ i.v. d 21-23, repeated after a therapy-free interval of 3 weeks for a total of 6 cycles. Since 1997 the same regimens were used in 12 patients (32.4%), while in the remaining 25 (67.6%) VACA alternating with IE (ifosfamide 1,800 mg/m$^2$ d 1-5 plus mesna, etoposide 100 mg/m$^2$ d 1-5) were administered every 3 weeks for a total of 17 courses. Relapsed patients were treated with second-line therapy with cisplatin-etoposide-ifosfamide or topotecan.

All patients in group A, 13 in group B and 7 in group C received radiotherapy to the primary tumor bed with doses ranging from 55 to 64 Gy as part of the treatment protocol. In all cases of fully or partially resectable tumor surgical treatment was offered to 12 patients from group A (60%), 15 from group B (68%) and 7 from group C (47%).

According to the European Group for Blood and Marrow Transplantation criteria, all high-risk patients must receive myeloablative chemotherapy with autologous HSCT. From our 37 high-risk patients treated after 1997, only 15 received myeloablative therapy. The remaining were not included in this program due mainly to a very rapid disease progression during conventional chemotherapy and unacceptable treatment toxicity or Karnofsky/Lansky performance status < 70%.

*Transplantation characteristics*

The patients were transplanted after a median of 10 months (range 8-18) from diagnosis, depending on the response to previous chemotherapy. Eight patients (53.3%) had received more than one line of conventional chemotherapy before transplantation.

*Stem cell harvest*

Autologous peripheral blood stem cells (PBSC) were mobilized with cyclophosphamide 2 g/m$^2$/d for 2 days and etoposide 100 mg/m$^2$/d for 3 days with G-CSF support 5 μg/kg/d s.c. until the last day of collection. PBSC collection was carried out using a Fresenius Hemo Care - Com. Tech. cell separator through a double lumen apheresis catheter one day after mobilization with leukocyte count over 1,500/mm$^3$, platelet count over 50,000/mm$^3$ and CD34+ count over 20/μl blood (on day +8 or +9 after the start of G-CSF). No purging was performed. The median collected amount of CD34+ cells was $6.37\times10^6$/kg (range 1.77 - 20) with median number of aphereses 2 (range 1-3).

*Conditioning regimens*

The patients were conditioned with chemotherapeutic preparative regimens. These included combination of several cytotoxic drugs without TBI. In 2 patients thiotepa (200 mg/m$^2$/d for 3 days) with cyclophosphamide (1,500 mg/m$^2$/d for 3 days) were given. The conditioning regimen for another 2 patients was ICE (ifosfamide 2,000 mg/m$^2$ i.v. d 1-6 with mesna, carboplatin 200 mg/m$^2$ d 1-6 and etoposide 250 mg/m$^2$ d 1-6). All other patients transplanted after 2004 received melphalan (140 mg/m$^2$/d, day 1) and busulphan (4 mg/kg/d for 4 days).

The transplantation was carried on day +2 after high-dose chemotherapy through central venous catheter. The median CD34+ cells transplanted were $4.49\times10^6$/kg (range 1.8-8).

*Supportive care*

Supportive care was given according to the institutional guidelines.

Prophylaxis for CMV and HSV-positive patients was with intravenous (i.v.) acyclovir. Broad-spectrum antibiotics were administered if fever developed during aplasia, and i.v. fluconazole (diflucan) if fever persisted despite the initial antibiotic therapy. Blood com-

ponent therapy was used to maintain the hemoglobin level above 8 g/dl and platelets above 20,000/mm$^3$; all cellular products were irradiated with 25 cGy. All patients received 10 μg/kg G-CSF, starting from day +3 until absolute neutrophil count (ANC) > $2.5\times10^9$/l on two consecutive days.

*Statistical analysis*

Kaplan-Meier curves were used to compute time to relapse or death. In each case survival interval was calculated from the date of diagnosis until the date of relapse/death, or the date of last follow-up. Recurrence or progression of disease or death from any cause was considered an event. Patients surviving without recurrence or progression were censored at the date of last contact. Comparison of survival between groups as a 95% confidence intervals (CI) was completed using log-rank test.

## Results

With a median follow-up of 48.9 months, group A patients had 25% OS and 15% DFS (Figures 1 and 2). Two from the patients treated between 1985 and 1997, both with bulky disease, had OS and DFS more than 15 years. In group B patients, after a median follow-up of 50.73 months (range 6-81), the OS was 27.27% and the DFS 18.8%. For group C patients with a median follow-up of 39.3 months (range 14-62), the OS was 33.3% and the DFS 20% (Figures 1 and 2). According to disease stage the survivors were distributed as follows: in group A - 3 patients with bulky disease, 1 with metastatic disease and 1 with relapse; in group B - 3 patients with bulky disease, 2 with metastatic disease and 1 with relapse; and in group C - 3 patients with bulky disease, 1 with metastatic disease and 1 with relapse.

No significant differences in OS and DFS among the 3 groups were detected (log rank, p=0.3).

From all transplanted patients, 13 were engrafted. The median engraftment time for neutrophils >500/mm$^3$ was 12 days (range 9-18) and for platelets >20,000/mm$^3$ it was 14 days (range 11-22). Two patients died in the transplantation unit without engraftment due to severe complications during aplasia (brain hemorrhage and multiorgan failure). The megatherapy-related mortality was 13.3%. Deaths occurred between days +22 and +45.

After transplantation 8 patients (53.3%) were rendered disease-free. No patient with progression (PD) achieved complete remission (CR), 1 achieved partial remission (PR), 1 died without engraftment, and 2 patients remained with PD. From patients transplanted in CR 1 died and 4 remained in CR. From patients transplanted in PR 2 achieved CR and 1 remained without change in disease status. The same results - 2 patients in CR and 1 without change -were registered in those transplanted in SD.

The main toxic manifestations from conditioning regimens were mucositis (grade II-III in 80% of the patients), fever in 73 (3%) and diarrhea in 66 (7%). All toxic complications were not severe and subsided after engraftment.

## Discussion

The prognosis of patients with metastatic or recurrent Ewing's sarcoma is poor and remains unchanged, despite treatment progress in the last years [13].

We reported on the outcome of high-risk patients with EFT who received conventional chemotherapy alone or conventional chemotherapy plus myeloablative chemotherapy for bulky, metastatic or recurrent disease in different historical periods of treatment efficiency.

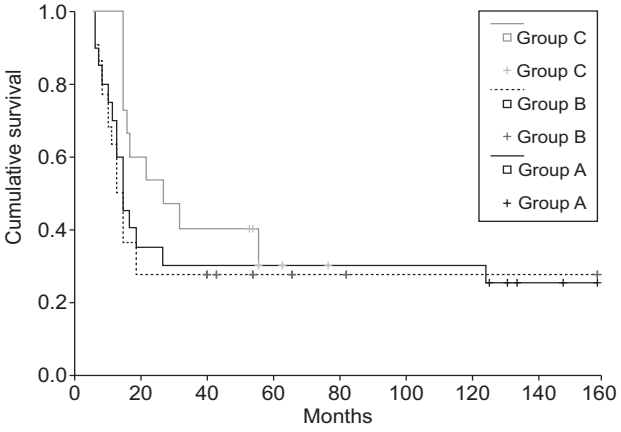


**Figure 1.** Overall survival of patients with EFT in 3 groups; p= 0.31.

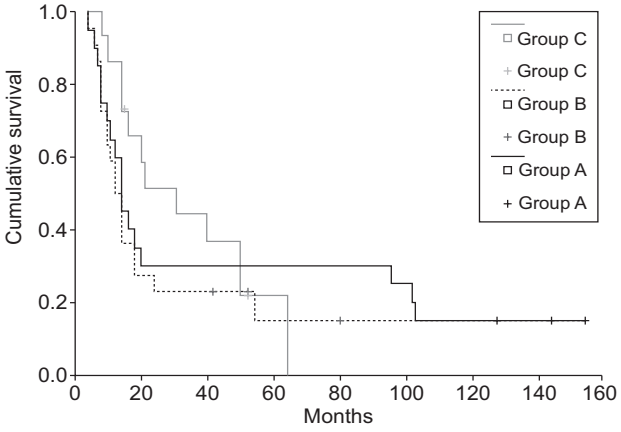


**Figure 2.** Disease-free survival of patients with EFT in 3 groups; p=0.58.

Between 1985 and 1997 all high-risk patients with EFT in our hospital were treated with classic conventional chemotherapy - VACA and VAIA regimens. OS and DFS of group A patients were similar to those reported in the literature - 25 and 15%, respectively. Many studies in this period reported results on survival of first-line treatment of poor prognosis EFT, ranging between 0 and 22% [5,8]. For patients with metastatic disease the survival rates were below 20% [14,15]. For relapsed patients with localized or metastatic disease at diagnosis the reported survival was even lower. Rodriguez-Galindo and colleagues from St. Jude's Hospital reported 5-year progression-free survival (PFS) of 18-22% for 71 patients with relapsed localized or metastatic Ewing's sarcoma treated between 1979 and 1999 [16]. Five-year PFS of a similar group of patients treated between 1985 and 2002 reported from CHMRC, Seattle was the same - 20% [17].

More intensive chemotherapy after the addition of ifosfamide and etoposide in the conventional treatment regimens has improved the survival rate of poor prognosis EFT patients, but their long-term outcome remains dismal. The OS and DFS of our patients with high-risk EFT treated with more intensive chemotherapy in the period between 1997 and 2010 were 27.3% and 18.8%, respectively. Compared with the earlier period, there was a minor gain in survival. The results are similar with those reported from other centres. Sari and colleagues from the Oncology Hospital in Ankara reported 5-year OS and EFS of 27% and 18%, respectively, in patients with metastatic disease treated with conventional chemotherapy between 1992 and 2005 [19]. Most authors reported 30-34% PFS for patients with metastatic disease and 14-15% for relapsed patients treated after the addition of ifosfamide and etoposide to conventional therapy [6,11].

Ewing's sarcoma and other EFT are considered chemosensitive neoplasms, which provides a rationale for high-dose chemotherapy as an initial treatment of metastatic disease or as salvage therapy for relapsed or refractory tumors. Most conditioning regimens have focused on melphalan with or without busulfan. Our results in patients with Ewing's sarcoma treated with myeloablative chemotherapy with autologous HSCT after conventional treatment are better than after conventional therapy alone, but without significant difference. These results are also similar to those reported from other transplantation centers. According to the results reported from Lashkari and colleagues from the City of Hope Comprehensive Cancer Center, OS and PFS of 30 patients with locally advanced or metastatic/recurrent Ewing's sarcoma treated with high-dose chemotherapy followed by autologous HSCT were 31% and 23%, respectively [19]. In the early studies in 1990s, when many centers used TBI in conditioning regimens, the survival results were not better [20]. On the other hand, multiple reports have documented the beneficial effect of HSCT in patients with EFT treated with conditioning regimens with melphalan. The French Society for Pediatric Oncology has reported excellent results in children with poor prognosis EFT who were treated with melphalan and busulfan. Thirty-four patients treated with this protocol had a 52% DFS at 3 years [21]. Another report from the same group showed OS and DFS of 38% and 37% respectively, in 75 patients treated with busulfan and melphalan [22].

The results from different studies have shown that the role of myeloablative chemotherapy with autologous HSCT in the treatment of poor prognosis EFT is controversial [13]. In our analysis the OS and DFS in transplanted patients were higher than in those treated in the same time period with conventional chemotherapy alone, but the difference was not statistically significant. The minor difference in survival between patients in group A and group B confirm the fact that the benefit of intensified therapy is mainly for patients with localized disease. The progress in survival for high-risk patients may come in the future from new therapeutic approaches based on the biological characteristic of the tumor - inhibition of the fusion gene EWS-FLI 1 or its protein product, inhibition of tyrosine kinases, exploitation of non-apoptotic cell death and interference with angiogenesis [1].

## Conclusion

According to the data of this study it can be concluded that patients with poor prognosis EFT, treated with more intensive chemotherapy, including myeloablative chemotherapy have better survival compared to historical data, but the benefit is not statistically significant. The rapidly growing understanding of EFT biology is a challenge for clinical trials and collaboration between centers and may lead to an enriched arsenal of diagnostic and therapeutic technologies for even more improved results in the treatment of these patients.

## References

1. Balamuth N, Wormer R. Ewing's sarcoma. Lancet Oncol 2010; 11: 184-192.
2. Grier HE. Ewing family of tumors: Ewing's sarcoma and primitive neuroectodermal tumors. Pediatr Clin North Am 1997; 44: 991-1004.
3. Paulussen M, Bielack S, Jurgens H et al. Ewing's sarcoma of the bone: ESMO clinical recommendations for diagnosis, treatment and follow-up. Ann Oncol 2008; 19(Suppl 2): ii97-ii98.

4. Delattre O, Zucman J, Plougastel B et al. Gene fusion with an ETS DNA-binding domain caused by chromosome translocation in human tumors. Nature 1992; 359: 162-165.
5. Rosen G, Wollner N, Tan C et al. Disease-free survival in children with Ewing's sarcoma treated with radiation therapy and adjuvant four-drug sequential chemotherapy. Cancer 1974; 33: 384-393.
6. Miser JS, Goldsby RE, Chen Z et al. Treatment of metastatic Ewing sarcoma/primitive neuroectodermal tumor of bone: Evaluation of increasing the dose intensity of chemotherapy - a report from the Children's Oncology Group. Pediatr Blood Cancer 2007; 49: 894-900.
7. Leavey P, Mascarenhas L, Marina N et al. Prognostic factors for patients with Ewing sarcoma (EWS) at first recurrence following multimodality therapy - a report from the Children's Oncology Group. Pediatr Blood Cancer 2008; 51: 334-338.
8. Bacci G, Mercuri M, Longhi A et al. Therapy and survival after recurrent Ewing's tumors: the Rizzoli experience in 195 patients treated with adjuvant and neoadjuvant chemotherapy from 1979 to 1997. Ann Oncol 2003; 14: 1654-1659.
9. Rosenthal J, Bolotin E, Shakhnovits M et al. High-dose therapy with hematopoietic stem cell rescue in patients with poor prognosis Ewing family tumors. Bone Marrow Transpl 2008; 42: 311-318.
10. Jaffe N, Paed D, Traggis D et al. Improved outlook for Ewing's sarcoma with combination chemotherapy (vincristine, actinomycin D and cyclophosphamide) and radiation therapy. Cancer 1976; 38: 1925-1930.
11. Grier H, Krailo M, Tarbell N et al. Addition of ifosfamide and etoposide to standard chemotherapy for Ewing's sarcoma and primitive neuroectodermal tumor of bone. N Engl J Med 2003; 348: 694-701.
12. Meyers P, Krailo M, Landy M et al. High - dose melphalan, etoposide, total-body irradiation, and autologous stem-cell reconstitution as consolidation therapy for high-risk Ewing's sarcoma does not improve prognosis. J Clin Oncol 2001; 19: 2812-2820.
13. Fraser C, Weigel B, Perentesis J et al. Autologous stem cell transplantation for high-risk Ewing's sarcoma and other pediatric solid tumors. Bone Marrow Transpl 2006; 37: 175-181.
14. Paulussen M, Ahrens S, Burdach S et al. Primary metastatic (stage IV) Ewing tumor: survival analysis of 171 patients from the EICESS studies. European Intergroup Cooperative Ewing Sarcoma Studies. Ann Oncol 1998; 9: 275-281.
15. Kolb E, Kushner B, Gorlick R et al. Long-term event-free survival after intensive chemotherapy for Ewing's family of tumors in children and young adults. J Clin Oncol 2003; 21: 3423-3430.
16. Rodriguez-Galindo C, Billups CA, Kun LE et al. Survival after recurrence of Ewing tumors; the St. Jude children's research hospital experience, 1979-1999. Cancer 2002; 94: 561-569.
17. Barker LM, Pendergrass T, Sanders J et al. Survival after recurrence of Ewing's sarcoma family of tumors. J Clin Oncol 2005; 23: 4354-4362.
18. Sari N, Togral G, Cetindag M et al. Treatment results of the Ewing sarcoma of bone and prognostic factors. Ped Blood Cancer 2010; 54: 19-24.
19. Lashkari A, Chow WA, Valdes F et al. Tandem high-dose chemotherapy followed by autologous transplantation in patients with locally advanced or metastatic sarcoma. Anticancer Res 2009; 29: 3281-3288.
20. Horowitz M, Kinsella T, Wexler L et al. Total-body irradiation and autologous bone marrow transplant in the treatment of high-risk Ewing's sarcoma and rhabdomyosarcoma. J Clin Oncol 1993; 11: 1911-1918.
21. Michon J, Hartmann O, Demeocq F et al. Consolidation with busulfan and melphalan followed by blood progenitor cell (BPC) graft in children and young adults with high-risk Ewing's sarcoma: a report of the French Society of Pediatric Oncology. J Clin Oncol 1994; 13: A1415.
22. Oberlin O, Rey A, Desfachelles A et al. Impact of high-dose busulfan plus melphalan as consolidation in metastatic Ewing tumors: a study by the Society Française des Cancers de L'Enfant. J Clin Oncol 2006; 24: 3997-4002.