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REVIEW ARTICLE

Is there a role of high dose chemotherapy and autologous stem cell transplantation in the treatment of Ewing's sarcoma and osteosarcomas?

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Summary

Although osteosarcomas are rare tumors, they are the most common primary bone tumors in children and adolescents younger than 20 years with a remarkable male predominance. Ewing's sarcoma (ES) is the second most common primary bone tumor in children and adolescents. The preferred actual treatment modality for osteosarcoma patients is neoadjuvant chemotherapy followed by complete surgical excision and adjuvant chemotherapy including agents such as doxorubicin, cisplatin, ifosfamide, and high-dose methotrexate which are widely used and accepted as being efficacious treatment strategies in osteosarcoma patients. Conventional treatments have increased overall survival (OS) rates in osteosarcoma and ES, but not as enough as desired. High dose chemotherapy (HDC) and autologous stem cell transplantation (ASCT) may be beneficial in some subgroup of ES, including children with partial response to conventional chemotherapy and with poor-risk as well as metastatic ES. HDC and ASCT remain as a clinical option in patients with ES, but it is considered as an experimental treatment approach for patients with osteosarcoma.

In this review, we discussed the current approach and role of HDC and ASCT in the treatment of osteosarcoma and ES and focused on the current literature data evaluating the treatment outcomes of some sub-groups of high risk patients.

Key words: *autologous stem cell transplantation, Ewing's sarcoma, high dose chemotherapy, osteosarcoma*

Introduction

Although osteosarcomas are rare tumors, they are the most common primary bone tumors in children and adolescents younger than 20 years (median age is 16 years) with a remarkable male predominance [1,2]. Osteosarcoma is exceptionally aggressive and primarily tends to metastasize to the lungs [3]. The second most common primary bone tumor in children and adolescents is ES with slight male predominance and may present atypically [2,4]. ES is a member of the Ewing sarcoma family of tumors (ESFT) with primitive neuroectodermal tumor (PNET) and Askin tumor [5,6]. Both osteosarcomas and ES include almost over 80% of all bone cancers among adolescents [2].

In the years that surgery was the only option for osteosarcoma patients, the 5-year OS rate was less than 10% [7]. Studies since those years had shown that almost all patients had subclinical metastatic disease even if there was no overt clinical metastasis at the time of diagnosis [8-10]. The preferred actual treatment modality for osteosarcoma patients is neoadjuvant chemotherapy followed by

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complete surgical excision and adjuvant chemotherapy including agents such as doxorubicin, cisplatin, ifosfamide, and high-dose methotrexate which are widely used and accepted as being efficacious treatment strategies in osteosarcoma patients [11-13]. This modality increased the 5-year OS to over 70% [9,10,14]. However, the outcome of treatment for recurrent or refractory osteosarcoma cases or for cases with overt metastasis during diagnosis is still poor [15].

Recently, a multimodality approach consisting of surgery, radiotherapy (RT) and intensified chemotherapy including ifosfamide and etoposide in addition to standard regimen with doxorubicin, vincristine, cyclophosphamide, and dactinomycin is preferred in the treatment of ES [16,17]. Although with current multimodality approach, 5-year OS rate increased up to 60-70% in patients with non-metastatic disease, and 5-year OS rates remain about 22% to 30% in patients with metastatic disease [17-19]. Besides, the treatment outcomes are still poor for patients older than 15 years or with large tumor volume or with poor histopathologic response after induction treatment [17,19-21].

HDC and ASCT have been extensively used for the treatment of various solid tumors, lymphomas and multiple myelomas since the beginning of 1990s [22-30]. In considering that HDC-ASCT related mortality rates due to regimen-related toxicities and transplant-related complications decreased to 1-2% in highly sophisticated transplant centers [31-34], this treatment modality now remains as an important tool for the treatment of lymphoma and multiple myeloma as well as germ cell tumors and some subgroups of high risk patients with osteosarcoma and ESFT/PNET [35-41]. Based on the European Bone Marrow Transplantation group (EBMT) database ESFT/PNET tumors are second only to germ cell tumors as the most frequent indications for HDC and ASCT [42].

With conventional treatment approaches in patients with osteosarcoma and ES, increased OS rates have been achieved compared to the past, but they have not reached to desired levels yet. Therefore, in this review we discussed the current approach and role of HDC and ASCT in the treatment of osteosarcoma and ES and we focused on the current literature data evaluating the treatment outcomes of some sub groups of high risk patients.

HDCT and ASCT in the treatment of osteosarcoma

Almost all published studies about the use of HDC and ASCT for the treatment of osteosarcoma have included only small number of patients with heterogeneous treatment regimens. Results of these studies should be evaluated with caution before determining a standard second-line therapy.

In a retrospective study conducted by Saurby et al. 15 high-grade osteosarcoma patients (9 male, 6 female; median age 17 years, range 7-26) who relapsed after chemotherapy and surgery and received HDC and ASCT were included [43]. The preparation regimens for HDC were heterogeneous. Median follow up was 16 months and 3 patients died of transplant-related mortality (TRM), one patient remained with persistent disease and 8 patients experienced further relapses and only 2 patients were in complete remission 36 and 48 months after HDC and ASCT. This study suggested that HDC and ASCT did not significantly improve the outcomes of patients with relapsed osteosarcoma compared to historical data of conventional treatment. However, conditioning regimens in this study were heterogeneous and the number of patients was small.

In a phase II study conducted by Arpaci et al. in Turkey, 22 high-grade, non-metastatic, primary osteosarcoma patients (19 male, 3 female), with age ranging from 15 to 27 years, underwent HDC and ASCT after receiving 2 cycles of induction chemotherapy including cisplatin, doxorubicin and ifosfamide [13]. All patients underwent surgery following HDC and ASCT and received 3 to 6 cycles of additional postoperative chemotherapy. No TRM was noted. Median follow up was 23.7 months (range 4.6-75.7) and metastasis had reportedly occurred in 23% of all patients and the earliest was in the 11th month. This study showed that 82% of all patients achieved greater than 90% tumor necrosis with neoadjuvant HDC. The OS and disease-free survival (DFS) rates at 1 year were 100% and 94%, respectively. The 3-year OS and DFS rates decreased to 83% and 70%, respectively. According to the results of this study, the authors suggested that neoadjuvant HDC may provide a greater than 90% necrosis rate with an acceptable toxicity and shorten the duration of therapy.

In another retrospective study, 19 high-risk osteosarcoma patients (13 male, 6 female) with median age of 12 years (range 6-20) were enrolled between 2006 and 2013 [44]. In this study, high-risk osteosarcoma was defined as the presence of one or more of the following factors: tumor necrosis less than 90% after neo-adjuvant chemotherapy, metastasis, and progression during therapy or relapse. All patients underwent HDC and ASCT with a uniform conditioning regimen including melphalan (140 mg/m^2 on day 7 and 70 mg/m^2 on day 6), etoposide (200 mg/m^2 from day 5 to day 8) and carboplatin (400 mg/m^2 from day 5 to day 8) (MEC) following neo-adjuvant chemotherapy, surgical re-

section and adjuvant chemotherapy. The OS was 78.3%, and the DFS was 67.4% at a median follow-up of 31 months (range 1-91). Relapse occurred in 26% of the patients at median of 9 months (range 3-15). One patient (5%) died of TRM. In a subgroup analysis including 8 patients, who were defined as high-risk osteosarcoma by the presence of tumor necrosis less than 90% after neo-adjuvant chemotherapy, OS was 100% and DFS was 87.5% at a median follow-up of 27 months (range 9–61). In high-risk osteosarcoma patients with two or more risk factors, DFS was significantly worse than in patients with only one risk factor (33.3 vs. 83.9%; p=0.019) [44]. Although the results of this treatment approaches were somehow promising, especially in high-risk osteosarcoma patients who had tumor necrosis less than 90% after neo-adjuvant chemotherapy, the results were discouraging for high-risk osteosarcoma patients with two or more risk factors. Considering that relapses were observed in one fourth of the patients, a single course of HDC and ASCT with MEC might be insufficient for a certain group of high-risk osteosarcoma patients with 2 or more risk factors [44].

Retrospective data reported by Demirer et al. covered the EBMT Solid Tumors Working Party (EBMT-STWP) between 1980-2001 and involved 254 evaluable patients with osteosarcoma (61 in CR and 172 in non-CR) who received HDC and ASCT with OS rates of 28% at 4 years' follow-up [45]. Median PFS in CR and non-CR patients at ASCT were 18 and 9 months, respectively. There was no difference between the two groups regarding 3-year PFS (p=0.2154; Figure 1) [45].

In conclusion, current data regarding the efficacy of HDC and ASCT in patients with osteosarcoma is not sufficient and does not support the use of such treatment modality on the basis of the presence of few retrospective studies with small number of patients and lack of prospective randomized studies. Therefore, the role of HDC and ASCT in patients with osteosarcoma remains as an experimental approach.

HDCT and ASCT in the treatment of Ewing's sarcoma

Feasibility of HDC and ASCT treatment was evaluated in many different groups of patients such as non-metastatic, metastatic, recurrent or progressive ESFT/PNET. However, studies evaluating the efficacy of HDC and ASCT in adult patient groups are very limited.

In a joint study conducted by the Italian Sarcoma Group (ISG) and the Scandinavian Sarcoma Group (SSG), 300 non-metastatic ES patients at a median age of 15 years (range 3-40) entered the study between 1999 to 2006 [46]. Thirty-eight percent of patients were adults (18 years or older). After initial chemotherapy regimen (with surgery and/or radiotherapy), patients were evaluated and divided into two groups as good responders (GR) and poor responders (PR) (n=154, 51%). The proportion of PR was higher among adult patients (age ≥18; GR, n=36, 32%; PR, n=77, 68%; p<0.001). One-hundred and twenty six of 154 PR patients received HDC and ASCT and no TRM was reported. For PR patients who received an intensified treatment with HDC, 5-year DFS rate was 72% (95% CI, 64-80%), which was similar to GR patients (5-year DFS, 75%). For PR patients who were administered standard chemotherapy, 5-year DFS rate was 33% (95% CI, 11-55%). Therefore, this study claimed that the use of HDC and ASCT in PR patients is feasible, effective and associated with a higher DFS compared to historical series. In a study conducted by Burdach et al. 17 patients with multifocal primary and early or multiple relapsed ES were treated with high dose chemoradiotherapy (12 Gy TBI + high dose melphalan and etoposide) and ASCT [47], in which the probability of DFS was 45% + 12% at 6 years after the last event before transplant, compared with 2% + 2% for the historic controls. Therefore, they concluded that high dose chemoradiotherapy and ASCT can improve the prognosis of multifocal primary and early or multiple relapsing ES [47].

In a retrospective study with one of largest cohort of adults, 46 localized or primary metastatic ES patients at a median age of 21 years (range 15-46) were enrolled between 1987 and 2000 [48]. Twenty-two percent of patients had metastatic disease at the time of diagnosis. Patients received induction chemotherapy, local treatment, adjuvant chemotherapy and alkylating agent-based HDC. No TRM was noted. The 5-year OS and PFS rates were 63% and 47%, respectively. Median survival time was 63 months and PFS 48 months. Five-year OS was 34% in patients with metastasis at diagnosis and 71% with initially localized disease (p=0.017). This study showed that HDC maintain a better long-term survival rate in adults with ES [45].

In a multivariate analysis which was conducted by Barker et al. in retrospectively identified 55 consecutive patients with relapsed ESFT, reduced risk of death was associated with response to second-line therapy, DFS >24 months and receiving HDC and ASCT [49]. Therefore, they concluded that HDC as consolidation therapy for relapsed ESFT seems to be associated with improved OS, even after adjusting for DFS and response to second-line treatment [49]. Oberline et al. published a study in 2006 with 97 untreated metastatic bone ESFT/

PNET patients with a median age of 12.3 years (range 0.2-25) [50]. Among them, 75 patients without persistent or progressive disease at metastatic sites before the planned date of HDC, received HDC and ASCT. The 5-year DFS was higher in those 75 patients (47%) compared to median 5-year DFS of the study group (37%). Patients with lung metastasis benefited more from HDC than patients with bone metastases without bone marrow involvement (DFS was 52% and 36%, respectively). Only one of 23 patients with bone marrow involvement survived [50]. According to published data, for patients with lung-only metastases or bone metastases, HDC and ASCT may provide additional benefits compared to conventional chemotherapy.

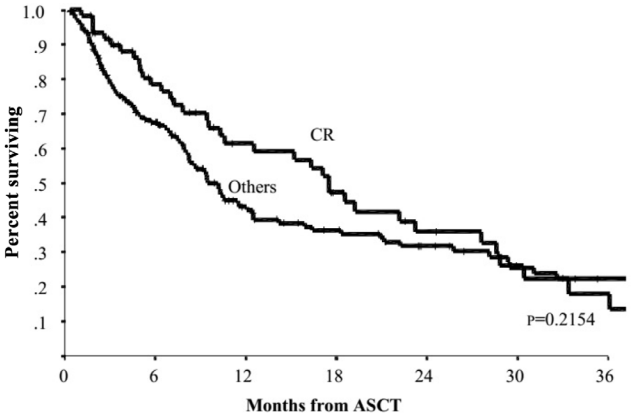

Figure 1. Progression-free survival after ASCT according to disease status at transplant for osteosarcoma patients.

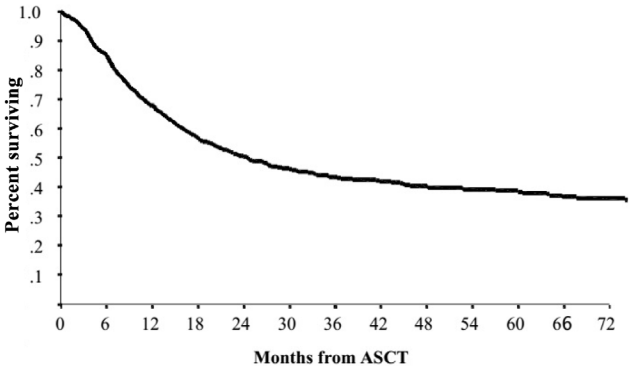

Figure 2. Overall survival after ASCT for Ewing's sarcoma patients.

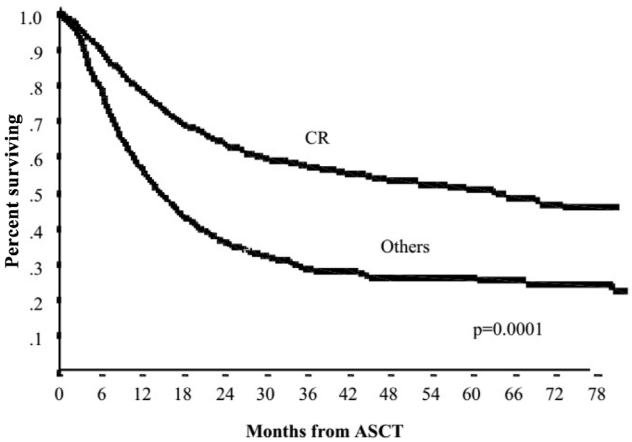

Figure 3. Overall survival after ASCT according to disease status at transplant for Ewing's sarcoma patients.

In another retrospective study conducted by Lamm et al. a total of 7 adult metastatic ES patients (5 male, 2 female) at a median age of 40 years (range 23-51) were evaluated [51]. Three of 7 patients had metastatic ES at the time of diagnosis and were treated with multiple chemotherapy regimens and 4 out of 7 patients with initially localized disease developed distant metastasis after receiving neoadjuvant chemotherapy, surgery/radiotherapy and adjuvant chemotherapy. Six patients received busulfan-melphalan and one patient received melphalan-etoposide as HDC. No TRM was recorded. The median OS rates for all patients (n=7), initial metastatic disease (n=3) and initial localized disease (n=4) were 22.3, 14.9 and 22.3 months, respectively. PFS for initial localized disease was 15.3 months (2.8–27.9). This study, despite having a small number of patients, showed that patients with metastatic ES benefited from HDC and ASCT [51].

In a single-center study conducted by Mc Tiernan et al. 33 patients with recurrent or progressive ES, with a median age of 19 years (range 7-33) were treated with HDC and ASCT as a second-line therapy [52]. Five-year DFS and OS were 38.2% (95% CI, 21-55%) and 42.8% (95% CI, 25-61%), respectively. Previously published studies showed that 5-year OS for patients with recurrent or progressive disease after first-line therapy ranged between 0 to 20% [53-55]. The results of this study also confirmed that duration of survival of patients in this group might be extended by HDC and ASCT.

According to the EBMT-STWP data reported by Demirer et al. between 1980-2001 1098 evaluable patients with ES (248 with sensitive relapse, 335 in first CR, 210 in first PR and 152 with either primary refractory, resistant relapse or 1st very good PR) received HDC and ASCT with an OS of 40% at 4 year follow-up (Figure 2), which was better than the OS of 28% at 4 years among patients with osteosarcoma [45]. ES patients in CR at ASCT did better than non-CR patients with a median survival of 64 and 15 months, respectively (p=0.0001; Figure 3).

In conclusion, based on the current accumulated literature data, HDC and ASCT may be beneficial in some subgroups of patients, mainly in children, with partial response to conventional chemotherapy, and with poor-risk as well as metastatic ES.

Therefore, HDC and ASCT remains as a clinical option in patients with ESFT/PNET for practising hematologists and oncologists in this field [46,50,56].

Overall conclusions

Based on the results of the above mentioned studies about the use of HDC and ASCT in the treatment of osteosarcoma are inconsistent. The main reason for this discrepancy is the different characteristics of the selected patient groups. Other reasons may be listed as small patient numbers, heterogeneous chemotherapy regimens used, and inadequate follow-up periods. While one study suggests promising results in high-grade, non-metastatic primary osteosarcoma [13], another study showed no significant improvement in the outcomes of relapsed osteosarcoma [43]. Similarly, in a study which was conducted by Hong et al. in high-risk osteosarcoma patients revealed that the benefit provided is only valid for one subgroup [44].

On the other hand, results of the studies about the use of HDC and ASCT in the treatment of ES are more coherent. Studies revealed that adult patients with ES [46], even with metastatic disease [50] or recurrent or progressive disease [52] may benefit from HDC and ASCT. Also, NCCN Guidelines (Version 2.2017) cited 3 studies and mentioned that HDC and ASCT has been associated with improved long-term survival in patients with relapsed or progressive ES in small, single-institution studies [47,49,52]. The retrospective EBMT data also support the use of HDC and ASCT as a clinical option in high risk ES patients. Although the results are promising, further, preferably, prospective studies with larger number of patients with longer follow-up periods should be conducted in order to evaluate the efficacy of HDC and ASCT in the treatment of ES.

Based on the current literature data, NCCN and EBMT guidelines, use of HDC and ASCT for treatment of some subgroups of high risk patients with ESFT/PNET remains as a clinical option but it is an experimental treatment approach for patients with osteosarcoma. Current literature data show that ES patients may benefit from HDC and ASCT much more than osteosarcoma patients. As a result, accumulated literature data do not support the use of HDC and ASCT in patients with osteosarcoma. We must emphasize that prospective randomized clinical trials are very crucial to document the efficacy of HDC and ASCT compared to conventional chemotherapy in ESFT/PNET patients, as well as to determine some specific subgroups of high risk patients, if any, who may benefit from this treatment modality.

Conflict of interests

The authors declare no conflict of interests.

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