

# Dose-Intensive Chemotherapy with Stem Cell Support as a Treatment Strategy for Bone and Soft-Tissue Sarcomas

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**Abstract:** Whether high-dose chemotherapy with stem cell support improves the long-term outcome for patients with bone and soft-tissue sarcoma is debatable and controversial. Prognosis of patients with unresectable or advanced metastatic sarcoma remains poor with a disease-free survival at 5 years less than 10 %; treatment is generally considered to be palliative. Doxorubicin, epirubicin and ifosfamide are the most active single agents with response rates above 20 %. Although drug combinations result in higher response rates, superiority against single agent chemotherapy in terms of survival could not have been demonstrated yet. As a dose-response relationship has been shown for the anthracyclines and especially for ifosfamide, high-dose chemotherapy with stem cell support has been evaluated by several investigators. However, all studies were not randomized, comprised small patient numbers and included heterogeneous histological subtypes of soft-tissue sarcomas. Nevertheless, higher doses of chemotherapy result in higher remission rates, which could correlate with longer survival. Well-designed randomized trials should be performed.

In this review article, we overview the literature and on the basis of our own data we emphasize the value of high-dose chemotherapy as a treatment option for younger patients with a good performance status in complete or partial remission prior to high-dose chemotherapy.

**Keywords:** Bone sarcomas, soft-tissue sarcomas, high-dose chemotherapy, stem cell support, positron emission tomography, review.

## BACKGROUND

Sarcomas are rare mesenchymal neoplasms that arise in bone and soft tissues. They constitute less than 1 % of all adult malignancies. Sarcomas affect all age groups; 15 % are found in children younger than 15 years old, and 40 % occur after the age of 55. Soft tissues include muscles, tendons, fat, fibrous tissue, synovial tissue, vessels, and nerves. Approximately 60 % of soft-tissue sarcomas arise in the extremities, with the lower extremities involved three times more often as the upper extremities. The incidence of adult soft-tissue sarcomas is approximately 2 per 100,000 population; bone sarcomas are even rarer with 0.5-2 per 100,000 population.

Currently, the prognosis of patients with unresectable or advanced metastatic bone and soft-tissue sarcoma remains poor with a disease-free survival at 5 years less than 10 %, mostly due to metastatic disease involving the lungs [1-6]. About 10 % of the patients present with metastatic disease at the time of diagnosis, whereas 40-60 % of patients with high-grade sarcoma will develop metastases despite local control of the tumor. Median survival from the time of diagnosis of metastatic disease is 8-12 months. Although treatment of advanced sarcomas is generally considered to be palliative, a small group of patients can be cured [6].

Doxorubicin and ifosfamide are the most active single agents in the therapy of sarcomas with response rates above 20 % [7-9]. For the anthracyclines and especially for ifosfamide a dose-response has been well documented [10-

13]. However, some active drugs, e.g. the anthracyclines, cannot be escalated due to their possible cardio-toxicity. In phase-II studies, different combination chemotherapy regimens based on high doses of ifosfamide, doxorubicin or cisplatin demonstrated response rates of up to 60 % [14, 15]. However, phase-III trials using these dose-intensive regimens demonstrated inconsistent benefits in terms of response rates, an improvement in overall survival could not be demonstrated [2-5].

There is no doubt that high-dose chemotherapy with hematopoietic stem cell support is currently not an established therapeutic option and has to be considered highly investigational. Therefore, it should not be performed outside clinical trials. Few data using high-dose chemotherapy in the treatment of Ewing's sarcoma, osteosarcoma and rhabdomyosarcoma demonstrated inconsistent benefits [16-20]. In several phase-I trials using high-dose chemotherapy in patients with different histology subtypes of adult soft-tissue sarcomas such as liposarcoma, leiomyosarcoma, and malignant fibrous histiocytoma, long-term survival has been reported for several patients [21-24], but long-term survivors have also been reported with conventional chemotherapy with or without resection [25]. Whether high-dose chemotherapy with autologous stem cell support improves the results in adult patients with bone and soft-tissue sarcoma is still debatable and controversially discussed [26].

In this review article, we give an overview on the literature concerning high-dose chemotherapy with stem cell support in the treatment of bone and soft-tissue sarcoma patients. On the basis of our own data we emphasize the value of high-dose chemotherapy as a treatment strategy for sarcomas. Furthermore, we demonstrate that a subgroup of

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patients in complete or partial remission prior to high-dose chemotherapy might derive benefit in terms of survival within the context of an interdisciplinary treatment approach.

## **DOSE-INTENSIVE CHEMOTHERAPY WITH STEM CELL SUPPORT**

### **Rationale and Prerequisites**

Investigation of high-dose chemotherapy became more interesting, as there has been a problem in finding new active substances in the treatment of bone and soft-tissue sarcomas. Of course, there are several conditions being necessary for the use of high-dose chemotherapy: there should be a chemo-sensitive tumor, a dose-response relationship for the active drugs, and no limiting non-hematological toxicity. Sarcomas and especially soft-tissue sarcomas can only be considered as moderately chemo-sensitive. Nevertheless, combination chemotherapy leads to frequent responses and complete responses of about 10 % are commonly achieved. For the anthracyclines and especially for ifosfamide a dose response has been well documented [10-13], but most studies used doxorubicin and ifosfamide combinations at suboptimal doses. More aggressive treatment strategies might result in higher overall response and higher complete remission rates. Therefore, it could be anticipated that a treatment strategy leading to higher rates of complete remissions might improve overall survival [27]. There is an even smaller chance of cure from metastatic disease [6, 25]. Myelo-suppression frequently occurs when using anthracyclines and ifosfamide at higher doses. Therefore, hematopoietic growth factors can be used or, when using even higher doses of the active chemotherapeutic agents, myelo-suppression has to be overcome by autologous stem cell support. Stem cell support is important in high-dose chemotherapy to overcome this myelo-suppression and to increase the dose of the chemotherapeutic agents; stem cell support becomes necessary, if the chemotherapy dose is so high and causes significant myelo-suppression. Meanwhile, the necessary armamentarium for the re-infusion of hematopoietic peripheral blood stem cells or bone marrow cells is well experienced. For the convenience of patients, collection and transplantation of peripheral blood stem cells is much easier than bone marrow harvest. Concerning non-hematological toxicity, there are several dose-limiting side effects such as mucositis, cardiotoxicity, nephro-toxicity and CNS-toxicity. For potentially curative situations, a type of chemotherapy resulting in a high number of responses would be the treatment of choice. Of course, the ideal patient for this kind of dose-intensive chemotherapy will be the younger otherwise healthy patient with a chemo-sensitive tumor likely to achieve complete remission following induction and high-dose chemotherapy. Based on these prerequisites, trials using higher doses of active chemotherapeutic agents were enrolled by several investigators and are summarized in the following literature section.

### **Published Literature**

Literature discussing the value of high-dose chemotherapy with peripheral autologous blood stem cell support in the treatment of bone and soft-tissue sarcomas is

scarce. The difficulties are based on rather small numbers of patients enrolled into the performed studies, by comparing different histologies or treatment strategies, and the complete lack of randomized trials.

For the bone sarcomas, Fagioli *et al.* included 32 patients with metastatic osteosarcoma in a phase-II study treating them with two cycles of high-dose chemotherapy with carboplatin and etoposide followed by stem cell support [19]. The overall survival at 3 years was 20 %, but the relapse rate was about 85 %. Although this group achieved high complete remission rates, the duration of remission was very short. Sauerbrey *et al.* treated fifteen children with relapsed osteosarcoma and could not demonstrate a significant survival benefit compared to conventional relapse chemotherapy [20]. Other studies reporting on the use of high-dose chemotherapy in the treatment of Ewing's sarcoma, osteosarcoma and rhabdomyosarcoma showed inconsistent benefits in terms of response rates and survival [16-18]. Recent reviews discussing extensively the use of high-dose chemotherapy with stem cell rescue for Ewing's sarcoma, rhabdomyosarcoma and osteosarcoma especially in pediatric patients could not demonstrate an unequivocal benefit [28-30].

For the soft-tissue sarcomas, Elias *et al.* analyzed ten patients in a phase-I trial. Four of eight evaluable patients responded with one complete remission in a patient with Ewing's sarcoma [31]. The same author summarized the data for high-dose therapy for adult soft-tissue sarcomas in terms of response and survival in a review article [32] and found that results from certain trials demonstrated improved, long-term, relapse-free survival compared with historical controls, whereas others suggested that selection biases may account for such improvements. Carefully designed randomized trials to evaluate the role of high-dose therapy with cellular support should be strongly encouraged in these histologies. Dumontet *et al.* treated 22 patients with different conditioning regimens. The overall response rate of nine evaluable patients was 66 % and the median survival and disease free survival were 19 and 15 months, respectively [23]. Blay *et al.* published the largest homogeneous study concerning this topic; they treated 21 patients with metastatic soft-tissue sarcomas using a high-dose chemotherapy regimen consisting of etoposide, ifosfamide and cisplatin [27]. They could demonstrate a median overall survival of 19 months and a progression-free survival of seven months. Of course, survival rates from the initiation of conventional chemotherapy were even longer, 26 and 14 months, respectively. The French group around Blay reported of yielded response rates after high-dose chemotherapy ranging between 18 and 66 %. Some of the patients with advanced stage soft-tissue sarcoma achieved a long-term complete remission, in particular the subgroup of patients in complete remission after conventional chemotherapy [33]. In another study, two of four patients consolidated with high-dose chemotherapy and stayed disease free at 41 and 27 months, respectively [24]. Bokemeyer *et al.* enrolled eighteen patients in a study administering cycles of doxorubicin and escalated doses of ifosfamide and stem cell support [21]. A response rate of 50 % including 22 % complete remissions was reported.

However, the median overall survival was only 13 months. Reichardt *et al.* treated 27 patients in a phase-II study with up to five cycles with increasing doses of epirubicin and ifosfamide followed by blood stem cell re-infusion. However, the response rate of 38 % was rather low [15].

There is a large database collected by the European Group for Blood and Marrow Transplantation (EBMT) including over 280 patients with soft-tissue sarcomas [34]. Nevertheless, more than 200 of these reported tumors are childhood rhabdomyosarcomas with a survival rate of 19 % at 5 years

**Table 1. Description of Patients' Characteristics (n = 30)**

Patient No.	Age at TPL [years]	Histologic subtype	Metastatic sites	Tumor and disease status prior HDCT		HDCT regimen	Current status	Survival after HDCT [months]
1	20	Ewing	pul	PR	up-front	Mel+Eto	NED	93+
2	22	Osteo	no	PR	up-front	ICE	DOD	27†
<b>3</b>	<b>19</b>	<b>Ewing</b>	<b>pul</b>	<b>CR</b>	<b>up-front</b>	<b>Mel+Eto</b>	<b>NED</b>	<b>70+</b>
4	36	Lipo	retroperit	PR	recurrence	ICE	DOD	11†
<b>5</b>	<b>17</b>	<b>Ewing</b>	<b>no</b>	<b>CR</b>	<b>up-front</b>	<b>Bus+Mel</b>	<b>NED</b>	<b>59+</b>
6	31	Meningo	pul	PD	progression	ICE	DOD	7†
7	22	Ewing	no	CR	recurrence	Bus+Mel	NED	56+
<b>8</b>	<b>21</b>	<b>Ewing</b>	<b>no</b>	<b>CR</b>	<b>up-front</b>	<b>Bus+Mel</b>	<b>DOD</b>	<b>30†</b>
9	42	RMS	BM	PR	up-front	ICE	DOD	6†
10	31	Osteo	pul	PD	progression	<sup>153</sup> Sa+CE	DOD	18†
11	13	Osteo	pul, bone	PR	recurrence	Mel+Eto	DOD	15†
<b>12</b>	<b>19</b>	<b>Ewing</b>	<b>bone</b>	<b>CR</b>	<b>up-front</b>	<b>Bus+Mel</b>	<b>NED</b>	<b>46+</b>
13	19	Osteo	pul	PD	progression	<sup>153</sup> Sa+CE	DOD	2†
14	20	MPNST	no	PR	recurrence	Mel	DOD	17†
<b>15</b>	<b>19</b>	<b>MPNST</b>	<b>no</b>	<b>CR</b>	<b>recurrence</b>	<b>ICE</b>	<b>AWD</b>	<b>36+</b>
16	33	MPNST	no	SD	recurrence	ICE	AWD	33+
<b>17</b>	<b>44</b>	<b>Osteo</b>	<b>no</b>	<b>CR</b>	<b>recurrence</b>	<b>Mel+Eto</b>	<b>NED</b>	<b>28+</b>
18	28	Ewing	no	PR	up-front	Bus+Mel	NED	28+
<b>19</b>	<b>33</b>	<b>Lipo</b>	<b>no</b>	<b>CR</b>	<b>recurrence</b>	<b>ICE</b>	<b>NED</b>	<b>26+</b>
<b>20</b>	<b>30</b>	<b>Ewing</b>	<b>pul</b>	<b>CR</b>	<b>up-front</b>	<b>ICE</b>	<b>DOD</b>	<b>7†</b>
21	21	Osteo	pul, skin	PD	progression	Bus+Mel	DOD	5†
22	34	Synovial	pul	SD	up-front	ICE	DOC	0†
23	53	Synovial	pul	PD	progression	ICE	AWD	14+
24	23	Synovial	pul, bone	PR	up-front	ICE	AWD	18+
25	56	Ewing	pul	PD	progression	Bus+Mel	DOD	4+
26	59	Leiomyo	pul	PR	up-front	ICE	AWD	16+
27	43	MPNST	no	PR	up-front	ICE	AWD	8+
28	39	Leiomyo	pul, liver	PR	up-front	ICE	NED	4+
<b>29</b>	<b>24</b>	<b>Chondro</b>	<b>pul</b>	<b>CR</b>	<b>up-front</b>	<b>ICE</b>	<b>NED</b>	<b>12+</b>
30	38	Synovial	pul	SD	recurrence	Mel	DOD	4†

**Abbreviations:** Osteo, osteosarcoma; Ewing, Ewing sarcoma family; Lipo, liposarcoma; Meningo, meningosarcoma; RMS, rhabdomyosarcoma; MPNST, malignant peripheral nerve sheath tumour; Synovial, synovial sarcoma; Leiomyo, leiomyosarcoma; Chondro, chondrosarcoma; pul, lungs; retroperit, retroperitoneal; BM, bone marrow; TPL, transplantation; Mel+Eto, melphalan 60 mg/m<sup>2</sup> + etoposide 1000 mg/m<sup>2</sup> day 1-3; ICE, ifosfamide 2000 mg/m<sup>2</sup>/day 1-6 + carboplatin 200 mg/m<sup>2</sup>/day 1-6 + etoposide 200 mg/m<sup>2</sup>/day 1-6; Bus+Mel, busulfan 600 mg/m<sup>2</sup> + melphalan 140 mg/m<sup>2</sup>; Mel, melphalan 200 mg/m<sup>2</sup>; <sup>153</sup>Sa+CE, <sup>153</sup>samarium + carboplatin 150 mg/m<sup>2</sup>/day 1-4 + etoposide 150 mg/m<sup>2</sup>/day 1-4; NED, no evidence of disease; AWD, alive with disease; DOC, died from other cause; DOD, died of disease; +, patient is still alive; †, patient died in this month

for the whole group and 31 % for the patients treated with high-dose chemotherapy as consolidation after reaching complete remission following conventional chemotherapy. However, these data are not comparable to adult soft-tissue sarcoma. Reichardt *et al.* have already well described in 2002 until that time published literature on high-dose chemotherapy with stem cell support focusing on the treatment of soft-tissue sarcomas [35]; They concluded that studies are usually small, and included very heterogeneous group of patients. Therefore, high-dose chemotherapy in soft-tissue sarcoma has to be considered highly investigational and should not be performed outside clinical trials.

### Own Data

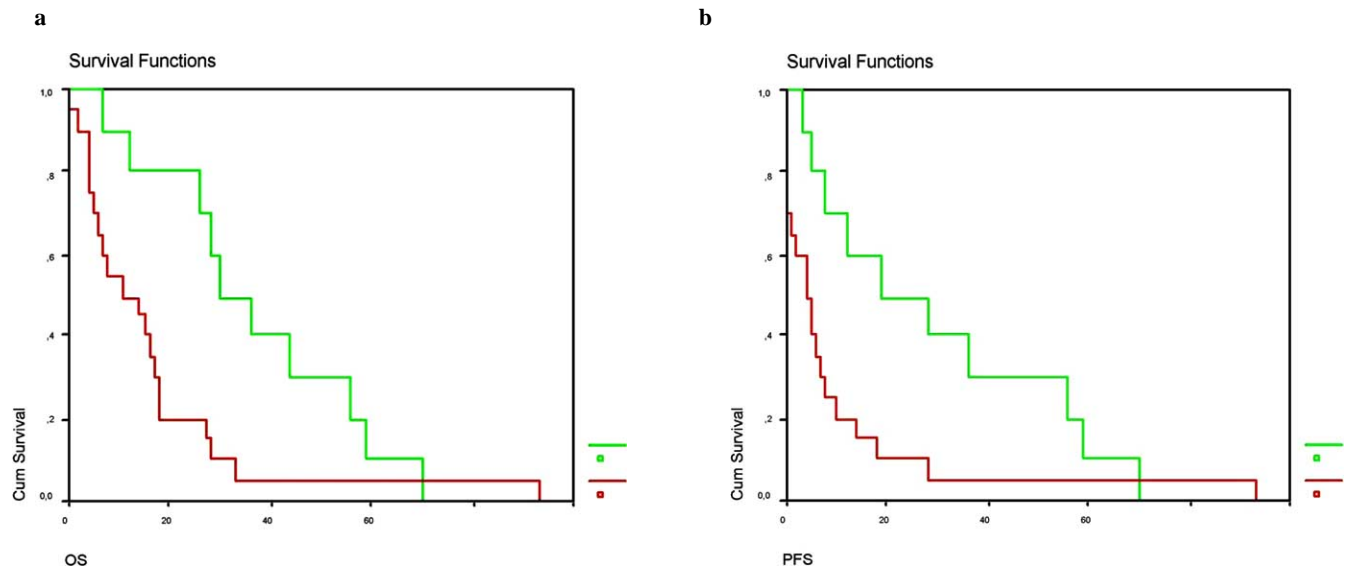
We analyzed the data of 30 patients with bone and soft-tissue sarcomas receiving high-dose chemotherapy with stem cell support between August 1998 and September 2004 at the Department of Internal Medicine V, University of Heidelberg, Germany. Patients' characteristics are summarized in Table 1. All histological diagnoses were reviewed by the local pathologist or by a reference pathologist according to multicenter studies. Histologies included the Ewing sarcoma family (n = 9), osteosarcomas (n = 6), chondrosarcoma (n = 1), malignant peripheral nerve sheath tumors (MPNST, n = 4), synovial sarcomas (n = 4), liposarcomas (n = 2), leiomyosarcomas (n = 2), rhabdomyosarcoma (n = 1) and meningiosarcoma (n = 1). Eighteen patients were female, twelve were male. Patients were mainly adult and aged between 13 and 59 years; median age at time of stem cell transplantation was 30.3 years. High-dose chemotherapy was performed in 14 patients up-front after induction chemotherapy; other patients received high-dose chemotherapy because of locally recurrent disease or progressive lung, bone or skin metastasis. Median CD34+ cell count at peripheral blood stem cell

transplantation was  $4.85 \times 10^6$  CD34+ cells /kg body weight [range: 2.0 – 16.7]. Following conventional chemotherapy and surgery, complete remission (n = 10), partial remission (n = 11) and stable disease (n = 3) were reached prior high-dose chemotherapy; six patients suffered from progressive disease.

For high-dose chemotherapy, the following conditioning regimens were used, partly according to multicenter studies such as CWS-96, EURO EWING 99, EICESS or COSS-96: The most established conditioning regimen was ICE/PEI consisting of ifosfamide 2000 mg/m<sup>2</sup> administered on day 1-6, carboplatin 200 mg/m<sup>2</sup>/day 1-6 and etoposide 200 mg/m<sup>2</sup>/day 1-6 (n = 15). Other melphalan-based regimens included melphalan 60 mg/m<sup>2</sup> plus etoposide 1000 mg/m<sup>2</sup> administered on day 1-3 (n = 4), melphalan 140 mg/m<sup>2</sup> plus busulfan 600 mg/m<sup>2</sup> (n = 7), or melphalan 200 mg/m<sup>2</sup> alone (n = 2). In two patients, a highly experimental regimen including samarium was used: <sup>153</sup>samarium + carboplatin/etoposide (carboplatin 150 mg/m<sup>2</sup> + etoposide 150 mg/m<sup>2</sup> administered on day 1-4).

All patients received an autologous peripheral blood stem cell graft and experienced WHO grade 4 leukocytopenia, neutropenia and thrombocytopenia. There was one sudden death due to cardiac arrest of unknown origin on day 7; autopsy was refused by the family (case 22). We observed no severe mucositis or infections WHO grade III-IV related to high-dose chemotherapy.

Median overall survival (OS) for all patients from the date of high-dose chemotherapy was 23.3 months [range: 0 – 93]; median progression-free survival (PFS) was 16.7 months [range: 0 – 93]. Ten patients (33 %) with complete remission before high-dose chemotherapy showed no evidence of disease after stem cell transplantation with a median PFS of 29.6 months [range: 3–70] and a median OS of 36.8 months [range: 7 –70]. Patients with progressive disease before high-dose chemotherapy did not benefit from



**Fig. (1).** (a) Overall survival (OS, months) of 10 CR patients (grey line) treated with high-dose chemotherapy and stem cell support in comparison to non-CR patients (black line).

(b) Progression-free survival (PFS, months) of 10 CR patients (grey line) treated with high-dose chemotherapy and stem cell support in comparison to non-CR patients (black line).

this strategy. Kaplan-Meier survival curves for OS and PFS of complete remission (CR) patients in comparison to non-CR patients are shown in Figs. **1a** and **1b**.

Interestingly, the bone sarcomas including the Ewing sarcoma family, osteosarcomas and chondrosarcoma (n = 16) demonstrated significant longer PFS and OS with 26.2 months [range: 0 – 93] and 31.1 months [range: 2 – 93] compared to the soft-tissue sarcomas (n = 14) with 5.9 months [range: 0 – 18] and 14.3 months [range: 0 – 36], respectively. Of course, that might be due to a significant longer follow-up for the bone sarcomas with a median of 31.3 months [range: 2 – 93] compared to a median of 14.3 months [range: 0 – 36] for the soft-tissue sarcomas, respectively.

Using positron emission tomography (PET) imaging, we evaluated response levels to induction chemotherapy to predict therapy outcome and whether patients are likely to achieve complete or partial remission before high-dose chemotherapy. We evaluated PET kinetics using fluorine-18 (FDG) in patients with high-risk soft-tissue sarcomas undergoing an induction chemotherapy consisting of anthracycline and ifosfamide prior to stem cell support. Our ongoing evaluation includes eight patients with 17 lesions. Seven out of eight patients were classified as grade III with lung or multiple metastases. All patients were examined prior to onset of induction chemotherapy and after completion of the first cycle. The dynamic series were performed over the area of the primary tumor (n = 5) or the lung metastases (n = 3). Following parameters were retrieved from the dynamic PET studies: SUV, fractal dimension, two-compartment model with computation of k1, k2, k3, k4 and vessel density. The FDG-influx was calculated using the rates of the two-compartment model and the formula  $(k1 \times k3) / (k2 + k3)$ . Discriminant analysis was applied for data analysis. Three patients showed progressive disease, one patient stable disease, one patient no evidence of disease and two patients a partial response. Due to the small number of patients, we dichotomized the data in patients with no evidence of disease/partial response (n = 3) and patients with stable disease/progressive disease (n = 4). Median SUV prior therapy was 8.3 in comparison to 4.3 SUV after one cycle of induction chemotherapy. Discriminant analysis using only the data of the initial FDG-PET study and a single parameter for input demonstrated the highest correct classification rate (CCR) for vessel density (73 %). Using the kinetic data only of the second study, CCR was equal for SUV, influx and fractal dimension (70 %). Best results were obtained for the combination of vessel density of the first study and either influx or fractal dimension of the second study with a CCR of 89 %. Taken together, the significance of vessel density calculated from the data of the initial PET study and the non-significance for the second PET examination direct to a major change in the angiogenesis within the initial phase of treatment. On the basis of these data, prediction of chemosensitivity of the tumor and moreover of the therapy outcome might be possible.

## DISCUSSION

High-dose chemotherapy has been studied only in small and inconclusive studies so far. Moreover, no randomized trials exist. Therefore, the use of high-dose chemotherapy for

locally advanced or metastatic adult sarcoma patients still remains highly investigational and should not be performed outside clinical trials [35, 36].

The median overall survival for all patients in our analysis was 23.3 months [range: 0 – 93] and the median progression-free survival was 16.7 months [range: 0 – 93]. Preliminary data were published by our group before [37, 38]. Our results are in line with the data of the French group around Blay [27]; we could even demonstrate longer survival compared to the published data with a median overall survival of 19 months and a progression-free survival of 7 months. Interestingly, Blay and co-workers found a significantly better outcome for the patients in complete remission before high-dose chemotherapy. We could validate these findings, as we could also demonstrate that patients in complete or partial remission before high-dose chemotherapy might derive benefit from this treatment strategy. One third of our patients showed no evidence of disease after stem cell support and consolidated with a median overall survival of 36.8 months [range: 7 – 70] and a median progression-free survival of 29.6 months [range: 3 – 70]. Therefore, our results suggest that high-dose chemotherapy may decrease the relapse rate and improve the survival of patients with bone and soft-tissue sarcomas in complete remission after conventional chemotherapy. Whether this regimen could also be applied to patients with complete remission after chemotherapy and surgery, or surgery alone, can neither be established on the basis of the present study, nor by other studies published in the literature so far. It cannot be concluded from the present data that high-dose chemotherapy does generally improve survival in patients in complete remission; improvement could only be due to a selection of favorable patients for this special treatment. The final answer to this question remains to be established through prospective, randomized trials.

The outcome of patients in partial remission or with a minor response before high-dose chemotherapy was less favorable. These observations suggest that high-dose chemotherapy may not be suitable for patients in less than complete remission. It cannot be excluded, however, that patients converted from partial to complete remission after high-dose chemotherapy may also benefit from this strategy. Patients with progressive disease before high-dose chemotherapy did not benefit from this strategy. This leads to the suggestion that high-dose chemotherapy should not be performed in patients with progressive disease or even stable disease.

Based on these findings, only soft-tissue sarcoma patients achieving complete or partial remission after conventional induction chemotherapy are treated with high-dose chemotherapy and stem cell support in our ongoing trial. In this trial we evaluate possible prognostic factors using positron emission tomography (PET) imaging. We evaluate response levels to induction chemotherapy, whether patients are likely to achieve complete or partial remission before high-dose chemotherapy. On that basis prediction of therapy outcome might be possible. Preliminary data are described in this review; they direct to a major change in the angiogenesis within the initial phase of chemotherapy treatment offering the possibility to predict whether the tumor is chemo-sensitive or not and whether the patient is likely to undergo high-dose chemotherapy or not.

So far, new therapeutic options are lacking. One possible new strategy analyzed by another group of our Department is the application of gene therapy for sarcoma. Transfer of the human multi-drug resistance 1 gene to normal hematopoietic stem cells and transplantation may significantly reduce the hematotoxicity of anthracycline or ifosfamide based chemotherapy. In addition, gene therapeutic strategies may also be used to directly target sarcoma cells, for example by transfer of suicide genes, a hypothesis which has been tested in an animal model system using non-obese diabetic-severe-combined immuno-deficient mice [39]. Of course, these preclinical findings have to be confirmed in prospective clinical trials.

## CONCLUSIONS AND SUMMARY

The published literature together with our retrospective results suggests that high-dose chemotherapy increases the complete remission rate of patients with bone and soft-tissue sarcoma. High-dose chemotherapy may also improve the survival of patients in complete remission, although this needs to be established through a randomized trial. In our as well as in other series, long-term survival after high-dose chemotherapy was rarely observed in patients presenting with less than complete remission. Therefore, this strategy remains palliative in most cases and still cannot be considered as standard treatment, compared with less intensive and less toxic conventional regimens. Possible candidates for high-dose chemotherapy are younger healthy patients with a good performance status in complete or partial remission prior to high-dose chemotherapy or those who are likely to achieve complete or partial remission undergoing surgery, preferably in the context of an interdisciplinary treatment approach.

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