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Current Controversies in Cancer

Should High-dose Chemotherapy be used in the Treatment of Soft Tissue Sarcoma?

P. Reichardt J. Verweij D. Crowther

Pro:

P. Reichardt

Department of Haematology, Oncology and Tumorimmunology, Robert-Rössle-Hospital, Virchow Medical Center, Humboldt University, Lindenberger Weg 80, D-13125 Berlin, Germany

'GRADE 3 nausea, vomiting, and myelosuppression or progressive, metastatic sarcoma?' This was the provocative title of an editorial by R. S. Benjamin in the *Journal of Clinical Oncology* in 1987 [1]. The author had analysed several clinical trials and stated that dose intensity resulting in more or less severe myelosuppression was a prognostic factor. He concluded that, for best results, the most active drugs should be given at doses high enough to produce myelosuppression.

In contrast to chemosensitive diseases such as lymphoma or breast cancer the number of active drugs against soft tissue sarcoma is very limited. Besides doxorubicin and epirubicin, only ifosfamide shows significant and consistent activity. The role of DTIC is questionable at least in non-leiomyosarcoma and the possible fourth drug, docetaxel, remains to be further investigated [2]. So far, new active drugs are not in sight. The only possibility of improving results is to optimise current treatment strategies, using the best drugs in the best possible way.

Doxorubicin [3, 4] and epirubicin [5–7] have been shown to have steep dose–response curves in different tumour types, including soft tissue sarcoma. A dose–response relationship has also been established for ifosfamide [8], high-dose ifosfamide being the only active drug in pretreated patients even after standard-dose ifosfamide [9–12]. Due to overlapping myelosuppression, most studies on combination chemotherapy used doxorubicin at doses below those in single drug therapy, thus compromising its activity.

Results of randomised studies comparing single-agent to combination chemotherapy are conflicting. In the three-arm study by the EORTC, doxorubicin at 75 mg/m^2 was compared to doxorubicin at 50 mg/m^2 together with ifosfamide 5 g/m^2 and the CYVADIC combination [13]. The response rates were generally low and no differences between the three treatment arms were observed, probably due to the decreased dose intensity in the combination arms. The ECOG conducted another three-arm trial with doxorubicin 80 mg/m^2 on the single-agent arm and dose reductions to 60 mg/m^2 and 40 mg/m^2, respectively, in combination with ifosfamide 7.5 g/m^2 or cisplatin and mitomycin C [14]. The ifosfamide-containing arm was significantly superior to doxorubicin alone in terms of response, but without a difference in survival. In view of the negative result of the EORTC study, it is important to keep in mind the higher doses of doxorubicin and ifosfamide in the ECOG two-drug combination.

With the introduction of haemopoietic growth factors into routine clinical practice it has become possible to combine drugs at their full single-agent doses. The first study using 75 mg/m^2 of doxorubicin in combination with ifosfamide and GM–CSF support was conducted by the EORTC and gave promising results compared with the previous experience of the group with lower dose combinations [15].

Considering all published studies with more than 20 patients using the combination of ifosfamide with either doxorubicin or epidoxorubicin, there seems to be at least a trend towards higher response rates for the higher dose regimens. Even more importantly, the rate of complete remissions lies consistently in the range of 10% and above (Table 1). Keeping in mind that approximately one-third of the complete responders have a chance of becoming long-term survivors [23, 24], this finding is especially important.

Only a few randomised trials comparing different dose intensities have been published to date. Bodey and associates used a protected environment to enable a higher dose of CYVADIC resulting in complete and overall response rates of 33% and 71%, respectively, compared with 15% and 67% for patients receiving standard-dose therapy [25]. Another study on different schedules of CYVADIC was conducted by the EORTC [26]. The results were a complete and overall response rate of 17% and 38%, respectively, for the full dose group, compared to 5% and 14% for the lower dose group. This was highly significant. The question of whether ifosfamide should be added to the combination of doxorubicin and DTIC was addressed by a large intergroup study accruing

Table 1. Response by drug dosage in combination chemotherapy for advanced soft tissue sarcoma

Author	Ifosfamide dosage g/m^2	Doxorubicin dosage mg/m^2	Epirubicin dosage mg/m^2	Growth factors	Response rate overall %	CR %
Mansi and associates, 1988 [16]	5	40			7	4
Santoro and associates, 1995 [13]	5	50			25	5
Schütte and associates, 1990 [17]	5	50			35	9
Frustaci and associates, 1993 [18]	9		75		28	9
Mansi and associates, 1988 [16]	5	60			41	9
Loehrer and associates, 1989 [19]	5	60			36	7
Edmonson and associates, 1993 [14]	7.5	60			35	5
Weh and associates, 1990 [20]	10	60			43	16
Toma and associates, 1993 [5]	6		50–100		42	11
Steward and associates, 1993 [15]	5	75		GM-CSF	45	10
Chevallier and associates, 1993 [21]	5		100–130		48	0
Frustaci and associates, 1994 [6]	9		100–140	GM-CSF	57	9
Reichardt and associates, 1995 [22]	12.5		90	G-CSF	52	21

340 patients [27]. Despite increased myelosuppression and infectious toxicity, the ifosfamide-containing arm was significantly superior in terms of response (32 versus 17%) and time to progression (6 versus 4 months). However, this increase in activity did not translate into a longer overall survival. A possible explanation seems to be the low number of complete remissions in these trials. Once this rate can be increased markedly, a positive impact on survival might occur. Another limitation is the rather small difference in the dose intensities used. In the recently reported randomised trial conducted by the EORTC, 75 mg/m^2 of doxorubicin plus ifosfamide with GM–CSF based on the favourable results from a previous study were compared to the lower dose combination. However, the dose increase in the investigational arm was only 50% for doxorubicin with unchanged ifosfamide dosage, hardly an overall difference that you could expect to result in a statistically significant improvement of survival. Furthermore, the study was hampered by a high percentage of leiomyosarcomas, a disease largely resistant to chemotherapy and therefore inadequate to prove the dose–response relationship. Nevertheless, the conclusion was that high-dose chemotherapy does not improve overall survival in advanced soft tissue sarcoma [28].

When considering high-dose chemotherapy, we should be aware of different concepts. High doses can be reached by either very high doses of drugs, normally several-fold the standard dose given once followed by bone marrow or stem cell reinfusion—as consolidation or 'up-front' treatment—or by multiple, relatively intermediate doses of chemotherapy given in a short time interval followed by growth factor or even stem cell support, a concept better referred to as dose-intensive chemotherapy.

In general, considering high-dose chemotherapy, several prerequisites are to be met:

(1) A chemosensitive tumour with at least some CRs following standard-dose chemotherapy;
(2) A dose–response relationship for drugs active against the tumour type;
(3) A dose–response relationship for the tumour type;
(4) No limiting non-haematological toxicity, thus allowing a major increase in drug dosage;
(5) A relevant question.

How does this apply to advanced soft tissue sarcoma?

Considering the single-agent activity of the most active drugs, soft tissue sarcoma can only be considered a moderately chemosensitive disease. However, when an anthracycline is combined with ifosfamide at a reasonable dose, responses do occur more frequently and complete remissions in the range of 10% are common. A dose–response relationship has been clearly shown for doxorubicin, epidoxorubin and ifosfamide and, furthermore higher doses of combination chemotherapy produce higher remission rates in metastatic soft tissue sarcomas. The dose-limiting toxicity of both the anthracyclines and ifosfamide is myelosuppression. Therefore, even when combining standard doses of both drugs, haematopoietic growth factors have to be used. With higher doses, especially of ifosfamide, prolonged thrombocytopenia occurs in up to 100% of patients thus warranting stem cell support. However, mucositis, cumulative cardiotoxicity and especially nephro- and CNS toxicities occur quite frequently at higher dose ranges. Therefore, approximately 2-fold doses of anthracyclines and 3-fold doses of ifosfamide are the upper limit in terms of non-haematological toxicity. Thus, major increases in dose over a short time period can only be reached by multiple-dose intensive courses of combination chemotherapy in the above-mentioned dose range. Furthermore, in contrast to childhood rhabdomyosarcoma, where complete remissions are quite common and high-dose consolidation concepts may apply, responses to standard-dose chemotherapy in adult soft tissue sarcoma are rather rare so that dose-intensive induction therapy seems to be the most promising approach.

The literature concerning high-dose chemotherapy with autologous bone marrow or stem cell transplantation in the treatment of soft tissue sarcoma is scarce and inconclusive for several reasons. First, there are no studies accruing high numbers of patients, and second, most of the reports mixed induction, intensification and consolidation strategies using various treatment protocols. Elias and associates [29] included 10 patients with sarcoma in a phase I trial evaluating high-dose ifosfamide and escalating doses of carboplatin with autologous bone marrow support of which 8 were evaluable for response. One longer-lasting complete remission in a patient with Ewing's sarcoma and 3 partial responses lasting approximately 10 months were observed. Dumontet and associates [30] treated 22 patients with various regimens and autologous bone marrow transplantation at different times during their disease. The overall response rate in 9 evaluable

patients was 66% and the overall median survival and disease-free survival were 19 and 15 months, respectively. Thirty-two per cent of patients were alive after 5 years. Kessinger and associates [31] reported on 13 patients treated with five different regimens. Four patients experienced a partial and 3 patients a complete response. Again, overall progression-free survival was rather short. A somewhat larger series was published by Blay and associates [32]. After response to conventional chemotherapy, 21 patients with metastatic soft tissue sarcoma received high-dose consolidation with etoposide, ifosfamide and cisplatin. The projected progression-free survival at 3 years was 28%. Another 4 patients consolidated with high-dose chemotherapy and autologous bone marrow rescue were reported by Mesia and associates [33], with 2 of them staying disease free at 41 and 27 months. Multiple cycles of full-dose doxorubicin in conjunction with escalated doses of ifosfamide and stem cell support have been investigated by Bokemeyer and associates [34]. The concept proved to be feasible but only preliminary data have been published to date. Most data have been collected by the EBMT registry, including 280 patients with soft tissue sarcoma. Two hundred and eight of the reported tumours are rhabdomyosarcomas, mainly in children, with a survival rate of 19% at 5 years for the whole group and 31% for those patients treated with high-dose chemotherapy as consolidation after reaching a complete remission following standard therapy [35]. Corresponding results have previously been published by the German–Austrian Pediatric Bone Marrow Transplantation Group with 6 out of 25 patients with metastatic rhabdomyosarcoma and 5 out of 11 patients with relapsed tumours transplanted in complete remission being disease free at a median observation time of 37 months [36].

Thus, in a very heterogeneous group of sarcoma patients, responses can be achieved with high-dose chemotherapy. Most patients, especially children with rhabdomyosarcoma, have been treated with high-dose consolidation therapy. Due to the lack of any randomised trials, no definite conclusions on a possible improvement in overall survival can be drawn so far. Generally, better defined inclusion criteria and more active regimens as outlined above will have to be used.

In conclusion, high-dose or dose-intensive chemotherapy for locally advanced or metastatic soft tissue sarcoma remains highly investigational. Yet the sound data on dose–response correlation and the possibility of reaching relevant increases in doses of drugs active against the disease support the hope for response rates high enough to translate into better overall survival. Certainly, the ideal patient for this type of therapy will not be the elderly with reduced performance status and high tumour load, but the younger otherwise healthy patient with a small but definite chance for long-term disease-free survival if achieving a complete remission. Finally, such a treatment strategy, once established in advanced soft tissue sarcoma, could be translated into the adjuvant situation for patients with large, deep-seated high-grade tumours with an otherwise more than 50% risk of dying due to widespread disease.

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Contra:

J. Verweij

Department of Medical Oncology, Rotterdam Cancer Institute (Daniel den Hoed Kliniek) and University Hospital, Groene Hilledijk 301, 3075 EA Rotterdam, The Netherlands

INTRODUCTION

SOFT TISSUE sarcomas are rare diseases comprising only 1% of all malignant tumours. As a consequence, the personal experience of physicians is usually limited with these tumours and treatment by multidisciplinary teams in specialised centres is therefore warranted. Studies have shown that multidisciplinary team discussions prior to the initial treatment of patients with soft tissue sarcomas result in a better treatment strategy and improved treatment outcome. Soft tissue sarcomas have a tendency to early haematogenous spreading and to control these distant metastases we obviously need effective systemic therapy. However, in view of the above mentioned team-dependent results of treatment as well as for other reasons, various single-centre studies may well result in a markedly different outcome. Firm conclusions on treatment strategies and projecting these to the world of common practice can only be based on multicentre studies of a large sample size. Bearing this in mind, the following will review the results of chemotherapy for metastatic soft tissue sarcomas.

STANDARD-DOSE SINGLE-AGENT CHEMOTHERAPY (TABLE 1)

Doxorubicin (DOX) was the first single agent found to be active in the treatment of metastatic soft tissue sarcomas, yielding response rates of 15–35% [1–6] in different studies. The most recent studies suggest a response rate to DOX of ± 20% when given as first-line chemotherapy.

In an attempt to reduce the toxicities related to DOX without reducing the activity, there has been extensive research on anthracycline analogues such as epirubicin. At equimolar doses the response rate to DOX (25%) was better than the response rate to epirubicin (18%) [7], but myelosuppression with epirubicin was less compared to DOX. All other anthracycline analogues and structurally related drugs unfortunately have been found to be inactive in soft tissue sarcomas.

One reason that most of soft tissue sarcoma patients do not respond to anthracyclines may be an overexpression of P-glycoprotein in association with the multidrug-resistant (MDR) phenotype [8, 9]. This observation limits the potential of high-dose anthracycline treatments in this disease.

The second active single agent in the treatment of soft tissue sarcomas is ifosfamide (IFOS). Initial studies with this drug were hampered by improper study designs but more recent phase II studies have proven the drugs' activity. IFOS given at a dose of 5 g/m^2 as 24 h infusion with concomittant mesna uroprotection yielded a response rate of 24% in non-pretreated patients [10, 11] while cyclophosphamide in this patient population was significantly less active [11]. The third