Chemotherapy for soft tissue sarcomas

Indications and advances

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Soft tissue sarcomas (STS) are uncommon tumors which arise from connective tissue and account for only approximately 1% of all malignancies. The term STS describes a heterogeneous group of tumors comprising about 30 different histological types, some of which are further subclassified. Low grade tumors generally carry a good prognosis with cure rates of 80–90 percent with local therapies. Conversely, high grade STS are characterised by a tendency to early micrometastatic disease, with at least half of all patients developing clinically evident metastatic disease despite adequate initial local therapy.

Chemotherapy has been used in STS in the preoperative, adjuvant and advanced disease settings. Clinical studies of chemotherapy in this disease are often difficult to interpret because of small patient numbers and heterogeneity of prognostic factors. For many of the important clinical questions adequate randomised studies have not been performed. In the treatment of individual patients therefore, the relevant clinical trial based objective data is often inconclusive.

These tumors occur in both children and adults, although the paediatric varieties are biologically different, tending to be more responsive to treatment, and should be considered separately. This review will focus on the evidence for the current role of chemotherapy in adult STS.

Prognostic factors for chemotherapy responce

A number of factors have been identified as potentially important in predicting response of adult STS to chemotherapy—these include tumor grade, S fraction, histological type, tumor site, age and performance status.

Studies looking at the ability of histological grade to predict chemotherapy response have shown conflicting results. This may be due to the use of different grading systems and the subjective nature of grading. A related but more accurate predictor may be S phase fraction. A study by Schmidt has shown high S phase fraction to be a significant predictor of chemotherapy response, but found no correlation for tumor grade (Schmidt et al. 1993).

The importance of histological tumor type in predicting response to chemotherapy also requires further evaluation, as most studies have been too small for subgroup analysis to be of value. In an EORTC overview of 1742 patients with adult STS treated with doxorubicin containing first line regimens, univariate analysis identified the presence of liposarcomas or synovial sarcoma as prognostic of response, but this was not borne out on multivariate analysis (Van Glabbeke et al. 1994).

Several studies have identified tumor site as prognostically important, with the presence of liver metastases indicating less likelihood of chemosensitivity (Van Glabbeke et al. 1994, Saeter et al. 1995). Older age and poor performance status have also been found to be negative predictors of chemotherapy response, probably because of decreased protocol adherence and a resultant decrease in delivered chemotherapy dose (Van Glabbeke et al. 1994).

Adjuvant chemotherapy

Although approximately 90% of all STS patients present with apparently localised disease, about half of these subsequently develop clinically evident distant metastases despite initial adequate local therapy (Yang et al. 1993). This sobering fact has lead to substantial efforts since the early 1970's to develop adjuvant systemic treatments to combat micrometastatic disease. Multiple prospective randomised trials of chemotherapy in this setting have been performed over the last 25 years but as yet no clear benefit for adjuvant chemotherapy has been demonstrated.

At least 11 prospective randomised trials of adjuvant chemotherapy for STS have been published (Table 1). 6 of these have evaluated single agent doxorubicin, and

Table 1. Randomised studies of adjuvant chemotherapy for adult STS

Reference	Treatment	No. of Patients	Median follow-up (months)	Relapse-free survival (%)	P value	Overall survival (%)	P value
Alvegard et al. 1989	D	77		62		75	
	Control	77	40	56	ns	70	ns
Gherlinzoni et al. 1993	D	32		56		NA	
	Control	44	106	25	0.02	NA	0.06
Eilber et al. 1988	D	57		58		84	
	Control	62	28	54	ns	80	ns
Antman et al. 1990[a]	D	80		67		68	
	Control	88	54	59	0.3	62	0.9
Chang et al. 1988	C, D, M	39		75		82	
	Control	28	85	54	0.04	60	0.1
Edmonson et al. 1984	C, D, V, ActD, DTIC	30		88		88	
	Control	31	64	67	0.08	82	0.6
Bramwell et al. 1994	C, D, V, DTIC	145		56		63	
	Control	172	80	43	0.007	56	0.6
Ravaud et al. 1990	C, D, V, DTIC	31		65		83	
	Control	28	52	37	0.003	43	0.002
Benjamin et al. 1987	C, D, V, ActD	20		54		65	
	Control	23	120	45	0.04	36	0.23

[a] Pooled data from 3 small studies.
D = doxorubicin, C = Cyclophosphamide, V = vincristine, ActD = actinomycin D, M = Methotrexate, DTIC = dacarbazine
ns= not significant, NA = not available.

the remaining 5, doxorubicin containing combination chemotherapy. 5 studies have shown significant differences in relapse-free survival (Gherlinzoni et al. 1993; Chang et al. 1988; Bramwell et al. 1994; Ravaud et al. 1994; Benjamin et al. 1987). In 2 of these, reported by Chang and Bramwell, the difference in relapse-free survival seen between the treated and control arms was mainly attributable to a decrease in local recurrences rather than metastases. Indeed, in only 2 studies did a difference in relapse-free survival correlate with a significant difference in overall survival. The first of these, reported by Gherlinzoni et al. (1993) and employing single agent doxorubicin was a relatively small study. It has been criticised because the randomisation may have been inadequate. There was a large imbalance in the number of patients between the two arms and the control group had an excess of patients with proximal tumors with a poorer prognosis. Indeed the relapse-free survival for control patients in this study is worse than for comparable control groups in other studies in Table 1. Similarly, the other study, reported by Ravaud (Ravaud et al. 1990), which showed a benefit in terms of overall survival for doxorubicin based combination therapy had small patient numbers and failed to adequately randomise patients according to known prognostic variables, resulting in a higher proportion of patients on the chemotherapy arm with more favourable extremity tumors.

Most of the randomised adjuvant studies have not had the statistical power to detect a real but moderate benefit of chemotherapy. The European Organisation for Research and Treatment of Cancer (EORTC) study (Bramwell et al. 1994) which is the largest published trial, should have been able to detect a 15% difference in overall survival between the treatment and control arms. However the adequacy of that study has been questioned for a number of reasons; a delay of up to 13 weeks between local therapy and institution of adjuvant chemotherapy was allowed, 48% of patients did not complete the intended therapy, and stratification factors such as tumor grade, known to be important in overall survival, were not accounted for in the trial design (Zalpuski et al. 1995).

In an attempt at producing a definitive study, an adjuvant trial in STS with an accrual goal of 450 patients was initiated in 1986 by the International Soft-Tissue Sarcoma Group (ISSG). The post surgery treatment arm consisted of 6 cycles of doxorubicin combination chemotherapy (MAID-mesna, doxorubicin, ifosfamide, dacarbazine). The study unfortunately closed after 18 months because of insufficient accrual (Zalpuski and Baker 1995)

Tierney et al. (1995) recently conducted a meta-analysis of the published trials of adjuvant chemotherapy in STS which recruited a total of 1546 patients. The results described a 41% reduction in the

risk of death at 5 years, corresponding to a 12% improvement in absolute survival. Although these results are encouraging, the authors warn that they should be interpreted with caution because of the biases inherent in an analysis based on data extracted from the literature. An international analysis of individual patient data has been initiated as a more reliable means of confirming this preliminary result and to examine whether any effect of adjuvant chemotherapy is consistent across disease sites, histological types, and grades of disease, and with tumor size and extent of resection.

Hence the role of adjuvant chemotherapy in STS remains unclear and awaits the results of further studies. Its routine use outside of a clinical trial setting can not be recommended.

Chemotherapy for metastatic disease

Once metastatic disease occurs in STS, the prognosis is poor. A small number of highly selected patients with isolated pulmonary metastases are candidates for metastatectomy which can result in 5 year survival rates in the order of 15–30% (Roth 1988; Martin and McCormack 1988). For the remainder, chemotherapeutic treatment results in tumor responses in 20–40% of patients, with less than 5% enjoying long term disease free survival (Antman and Elias 1988).

Single agent chemotherapy

Doxorubicin and ifosfamide have the highest single agent activity of established cytotoxics in advanced STS. Doxorubicin induces objective responses in 15–30% of patients (Antman and Elias 1988). Adequate dosing is important, with doses of 60–70 mg/m^2 three weekly superior to doses of 50 mg/m^2 or less (Demetri and Elias 1995). Other anthracyclines such as epirubicin have been studied but do not appear to have a therapeutic advantage over doxorubicin (Chevallier et al. 1990). Ifosfamide has higher single agent activity in STS than it's parent compound, cyclophosphamide (Bramwell et al. 1987). Studies have shown response rates of 7–38% in previously treated STS (Antman and Elias 1988), including responses in patients who have failed doxorubicin-containing regimens (Antman et al. 1989).

Other agents such as dacarbazine (DTIC), actinomycin D, methotrexate and vincristine have less efficacy in STS with response proportions less than 20%. Etoposide given as a short term infusion has shown minimal activity in STS. A recent phase II study however suggests significant activity for this highly cell-cycle specific agent when given as a continuous 72 hour infusion (Saeter et al. 1995).

Combination therapy

Most studies of combination chemotherapy in STS have taken doxorubicin as the most active single agent and added other active drugs in an attempt to increase response rates. Although high response rates have been seen in single arm studies of combination therapy, most large randomised co-operative group studies have reported response rates of only 17–30% with no significant survival advantage (Zalpuski and Baker 1995).

Three randomised trials have examined the addition of DTIC to doxorubicin, revealing enhanced response rates but no improvement in survival with the combination (Omura et al. 1983; Borden et al. 1987; Benjamin et al. 1978).

The Southwest Oncology group evaluated the addition of other agents to doxorubicin and developed the CYVADIC regimen consisting of cyclophosphamide, vincristine, doxorubicin and DTIC, with studies showing impressive response rates of 30–50%. A subsequent randomised study by the EORTC, however, was unable to demonstrate a significant difference between CYVADIC and doxorubicin alone (Santoro et al. 1990).

More recently the focus has shifted to the use of combinations of doxorubicin and ifosfamide. The MAID regimen (mesna, doxorubicin, ifosfamide and dacarbazine), developed at the Dana-Farber Cancer Institute, resulted in a 47% response rate with 10% complete responses in a phase II study of 105 patients (Elias et al. 1989). This regimen has not been compared to doxorubicin alone in a randomised study.

ECOG has performed a randomised study of doxorubicin alone, doxorubicin with ifosfamide and doxorubicin with cisplatin and mitomycin C (Edmondon et al. 1993). The doxorubicin dose was 80mg/m^2 on the single agent arm but only 40 or 60mg/m^2 on the combination arms because of additive myelotoxicity. In 262 patients response rates were 20%, 34% and 32%, respectively in the three arms. However, once again no survival difference was demonstrated.

Thus, although combination chemotherapy in STS results in higher tumor response rates than single agent therapy, there is no definitive evidence of a survival advantage. In patients with incurable metastatic STS, there is currently little data on quality of life and the subjective clinical significance of achieving an objective tumor response. It would be useful to incorporate quality of life outcome measures into subsequent clinical trials, particularly those looking at combination therapy, to clarify whether the increased toxicity of such regimens is offset by clinical benefit (Demetri and Elias 1995).

Dose intensive chemotherapy

There is consistent evidence of a dose-response relationship in STS for both doxorubicin and ifosfamide within the range of conventional dosing (Demetri and Elias 1995). Greater levels of chemotherapy dose intensification in STS can be achieved by the addition of haematopoietic cytokines or autologous stem cells. With such an approach non-haematological toxicities—such as mucositis and cardiac toxicity for doxorubicin, or renal and CNS toxicity for ifosfamide—ultimately become dose limiting.

The EORTC has shown that higher doses of doxorubicin (75mg/m^2) in combination with ifosfamide 5gm/m^2, can be given safely with haematopoietic cytokine support, with a response rate of 45% in 104 patients (Steward et al. 1993). A randomised phase III study is now underway comparing the above regimen with standard dose doxorubicin and ifosfamide. There is little published data on high dose chemotherapy with autologous stem cell support or bone marrow support in adult STS. A number of small non-randomised studies have shown reasonable response rates, but with disappointingly short median survival times (Kessinger et al. 1994; Elias et al. 1991).

In summary, dose intense chemotherapy within the conventional dosing range may be beneficial but there is no definite evidence of benefit from very high dose chemotherapy requiring haemopoietic stem cell support available to date.

New drug treatments

Medical therapy of STS remains unsatisfactory. Only two agents, doxorubicin and ifosfamide, consistently produce response rates in excess of 20% in advanced disease when used as single agents. As noted, although drug combinations improve the frequency of response, they do not appear to improve overall survival. Certainly no chemotherapy regimen has been shown to be curative. Clearly there is a need to identify effective new agents. Although many new drugs have undergone phase II testing in STS in the last 5 years, only docetaxel (Taxotere) has been shown to have reasonable activity, with lesser activity demonstrated for two other agents, edatrexate and topotecan.

Docetaxel is a semi-synthetic taxoid derived from the needles of the European yew tree. It has a novel mechanism of action by enhancing microtubule assembly preventing cell division during mitosis. A phase II study in previously treated STS has been performed by the EORTC Soft Tissue and Bone Sarcoma group (van Hoesel et al. 1994). Docetaxel was given at a dose of 100mg/m^2 in a 1 hour intravenous infusion 3 weekly. In 29 evaluable patients, 5 partial responses were seen. Further studies are currently in progress to evaluate the activity of this drug in previously untreated patients. The related taxoid drug, paclitaxel, has recently demonstrated a lack of activity in a phase II study in STS at a dose of 250mg/m^2 by 3 hour infusion with cytokine support (Sugerman et al. 1996).

Edatrexate is a methotrexate analogue which is more effectively transported and polyglutamated (a major mechanism of resistance for STS in vitro to methotrexate). In a phase II study of 34 evaluable and previously untreated patients, the drug was given at 80mg/m^2 weekly for 5 weeks and biweekly thereafter. 5 partial responses were obtained (Casper et al. 1993). A disease specific phase I study of high dose ifosfamide and edatrexate has recently been reported in abstract form, with the authors suggesting this may be a useful combination to develop for neoadjuvant or adjuvant trials (Sugerman et al. 1996).

Topotecan is a semi-synthetic derivative of the alkaloid, camptothecan, derived from the wood of the native Chinese tree Camptotheca acuminata. This is a new class of drugs which act by inhibiting topoisomerase 1, an enzyme which transiently breaks single strand DNA, thereby reducing torsional strain and unwinding DNA ahead of the replication fork (Hawkins 1993). A phase II study of this drug administered at 1.5mg/m^2 daily for 5 days every 3 weeks to 29 patients with STS resulted in 3 partial responses (Bramwell et al. 1995). Other topoisomerase 1 inhibitors are also under development.

Biological responses modifiers have also been investigated in STS. Preliminary trials with interleukin 2 and interferons have reported little or no activity (Salem et al. 1991). Closed circuit perfusion with tumor necrosis factor-alpha has been used with promising results in locally advanced tumors—in some cases allowing limb sparing surgery in patients who would otherwise have required amputation (Eggermont et al. 1992). The mechanism probably involves obliteration of tumor vasculature rather than a cellular anti-tumor effect.

Preoperative chemotherapy

There are no published randomised trials examining the role of preoperative chemotherapy in adult STS. The rationale for such an approach is that systemic treatment for potential metastases is instituted sooner, large tumors may become more amenable to resection, and additional post-surgical chemotherapy can be guided by the preoperative tumor response.

A retrospective review of the MD Anderson experience in which 46 of a total 396 patients were treated

with preoperative chemotherapy, showed an overall response rate of 40% and improved survival (60 vs. 33 months) for the preoperatively treated group (Pezzi et al. 1990). This data is difficult to interpret as it is likely that the patients were highly selected. The histological response to preoperative chemotherapy was a strong predictor of eventual outcome with significantly improved overall survival rates in those patients who responded (60% compared to < 20%).

The main potential role of preoperative therapy may be to enable limb salvage surgery in patients who would otherwise require amputation. Since 1974, sequential studies from UCLA in extremity adult STS using preoperative radiation and chemotherapy have shown an improvement in local control rate and reduction in amputation rates. An increasing emphasis on the chemotherapeutic component has been associated with a trend towards improved survival in recent years (Eiber et al. 1993). Other groups have shown good results in terms of limb salvage with the use of chemotherapy alone (Priebat et al. 1994).

Clearly at this time the optimal preoperative regimen is unknown and further studies using the most active agents are required. A SWOG study of preoperative MAID chemotherapy is underway. Patients are treated with 3 cycles of MAID prior to surgery. Responders and those with stable disease receive an additional 3 cycles of MAID after surgical resection. Patients with less than a wide resection undergo radiotherapy to the tumor bed. This trial is examining novel prognostic factors including tumor DNA content, cytogenetics and P-170 glycoprotein expression from tumor specimens (Zalupski and Baker 1995).

Conclusion

Chemotherapy is indicated in STS for selected patients in the preoperative and advanced disease settings while its role as adjuvant therapy awaits further clarification. Unfortunately only a few drugs have been shown to have useful activity in STS. Although drug combinations have improved response rates, such an approach has not had a clear impact on survival. Further well designed, large multicentre studies are required to determine the optimal treatment strategies for adult STS. Future directions will include evaluation of the activity of new drugs and drug combinations, as well as incorporation of biological predictors of response and "non-traditional" clinical outcome measures such as quality of life.

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