The Oncologist®

Sarcomas

Should Patients with High-Risk Soft Tissue Sarcoma Receive Adjuvant Chemotherapy?

SCOTT M. SCHUETZE,[a] SHREYASKUMAR PATEL[b]

[a]University of Michigan, Ann Arbor Michigan, USA; [b]MD Anderson Cancer Center, University of Texas, Houston, Texas, USA

Key Words. Soft tissue sarcoma • Adjuvant • Neoadjuvant • Chemotherapy

Disclosures

Scott M. Schuetze: None; **Shreyaskumar Patel:** *Honoraria:* Novartis, Amgen.

Section editors **Laurence Baker** and **Jaap Verweij** have disclosed no financial relationships relevant to the content of this article.

The content of this article has been reviewed by independent peer reviewers to ensure that it is balanced, objective, and free from commercial bias.

LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. Describe the type of patient with soft tissue sarcoma most likely to benefit from adjuvant chemotherapy.
2. Select the chemotherapy regimen most likely to benefit a patient with high-risk soft tissue sarcoma.
3. Evaluate the impact of adjuvant chemotherapy on risk of soft tissue sarcoma recurrence analyzed in the sarcoma meta-analyses.

ABSTRACT

Soft tissue sarcoma is a malignant connective tissue tumor that may arise anywhere in the body and from diverse mesenchymal elements. Its incidence is approximately 30 per million persons. The majority of patients with soft tissue sarcoma present with potentially life-threatening disease, and complete resection to obtain specimen margins free of tumor and radiation offer the best chance for local disease control. The risk of relapse and death from disease rises with increasing tumor stage, grade, and size. Adjuvant chemotherapy has been studied as a means to decrease the risk for disease recurrence in patients with localized soft tissue sarcoma at diagnosis, but the majority of trials reported on have been hampered by patient heterogeneity, low patient accrual, and short follow-up. Meta-analysis and reviews of institutional large series, in efforts to overcome some of the limitations, suggest that doxorubicin with ifosfamide reduces the risk for sarcoma recurrence and death in selected patients with high-grade, large, and chemotherapy-sensitive sarcoma subtypes to a clinically meaningful degree. In multiple analyses, patients with high-risk soft tissue sarcoma treated with chemother-

Correspondence: Scott Schuetze, M.D., Ph.D., University of Michigan, C342 Med Inn, SPC 5848, 1500 E Medical Center Drive, Ann Arbor, Michigan, 48109-5848, USA. Telephone: 743-936-0453; Fax: 734-647-7279; E-mail: scotschu@umich.edu Received January 15, 2009; accepted for publication September 4, 2009; first published online in ***The Oncologist*** *Express* on October 6, 2009. 1083-7159/2009/$30.00/0 doi: 10.1634/theoncologist.2009-0007

apy have a >10% absolute lower risk for disease recurrence and longer disease-specific survival than patients treated without chemotherapy. In the absence of conclusive results from an adequately powered, randomized, controlled clinical trial, the available data support the use of chemotherapy in the management of high-risk, localized, soft tissue sarcoma. ***The Oncologist*** 2009; 14:1003–1012

Introduction

Is there reasonable medical justification for offering patients diagnosed with high-risk soft tissue sarcoma adjuvant chemotherapy? This question has been debated for >20 years, with many authors concluding that study results and analyses are inconclusive because of faulty study design, inadequate statistical power resulting from small study size, short follow-up, bias from enrollment of patients with lower-risk sarcoma, and/or poor quality of data. Herein, we argue that sufficient evidence exists to recommend chemotherapy to selected patients diagnosed with high-risk, localized soft tissue sarcoma as a maneuver to decrease the risk for recurrence and early death from disease. We do not review clinical management of the pediatric rhabdomyosarcomas (alveolar and embryonal) and extraskeletal Ewing's family of tumors, for which chemotherapy is a recognized vital component of appropriate care. Gastrointestinal stromal tumors, a sarcoma of the gastrointestinal tract with unique biology rendering the tumor susceptible to growth inhibition by receptor tyrosine kinase inhibition and now managed differently than most other soft tissue sarcomas, are not discussed herein.

Clinical management of patients with soft tissue sarcoma is complicated by the large heterogeneity of the natural history of the disease. More than 50 subtypes of soft tissue tumors are recognized in the World Health Organization classification of tumors of soft tissue [1]. Sarcomas may arise anywhere in the body; therefore, multidisciplinary management requires broad expertise in surgical, orthopedic, medical, and radiation oncology. Patient outcomes are likely influenced by the level of experience of the treating physicians in managing sarcomas; patients treated at centers with a special emphasis in sarcoma management seem to have a lower risk for disease recurrence and longer survival [2]. We know that certain subtypes, for example, alveolar soft part sarcoma and clear cell sarcoma, have protracted clinical courses and/or relative resistance to traditional cytotoxic chemotherapy. In addition, recent advances in the knowledge of sarcoma pathophysiology and diagnosis, such as the identification of gastrointestinal stromal tumor as a distinct entity from gastrointestinal leiomyosarcoma, has likely changed the population of patients studied over time in clinical trials of adjuvant chemotherapy and influenced the results. Cure rates may be overestimated by inclusion of subtypes such as synovial sarcoma that can recur >10 years after definitive treatment, because the mean length of follow-up in many studies is <10 years. Thus, heterogeneity of disease and study populations heavily bias broad conclusions of chemotherapy benefit for patients with soft tissue sarcoma.

Over 10,000 people are diagnosed with soft tissue sarcoma in the U.S. each year and about 40%–50% die from the malignancy [3, 4]. More than half of the patients with soft tissue sarcoma have localized disease at the time of diagnosis. High tumor grade, large tumor size, and tumor involvement through or below the fascia are well established prognostic factors for disease recurrence and death after definitive local control of limited soft tissue sarcoma (Table 1) [5–7]. More than one half of the patients with high-grade soft tissue sarcomas >10 cm involving deep structures develop metastasis, usually involving the lungs, after local therapy to the primary disease site, and the majority of patients with distant relapse die from their disease [8]. The impetus for continued study of adjuvant therapy for soft tissue sarcoma stems from the high rate of fatality from relapsed disease and greater impact on society, because younger individuals are disproportionately more affected than with epithelial cancer.

Early Adjuvant Chemotherapy Sarcoma Studies

Doxorubicin was identified as an active anticancer agent in patients with advanced soft tissue sarcoma in the 1970s [9, 10]. Ifosfamide added to doxorubicin demonstrated a higher objective response rate of advanced/metastatic sarcoma than doxorubicin alone and is considered a contemporary combination chemotherapy for soft tissue sarcoma [11].

Rosenberg and colleagues at the National Cancer Institute performed a randomized trial between 1977 and 1981 of adjuvant doxorubicin, cyclophosphamide, and methotrexate in 65 patients with high-grade soft tissue sarcoma of the extremity [12]. There was an imbalance in sarcoma subtypes randomized to the chemotherapy versus "control" arms and the median follow-up time of about 2 years at the time of the report was short; however, significantly fewer patients who received chemotherapy had a sarcoma relapse (three versus nine) and death from disease (one versus

Table 1. Five-year survival rates in patients with localized soft tissue sarcoma

Variable	Metastasis-free survival	Overall survival
Tumor size		
<5 cm	82%	84%
5–10 cm	65%	76%
>10 cm	56%	59%
Tumor grade		
Low	92%	95%
High	63%	64%
Tumor depth		
Superficial	89%	90%
Deep	64%	67%
AJCC stage		
I		96%
II		78%
III		51%

Abbreviation: AJCC, American Joint Commission on Cancer.
Adapted from Pisters PW, Leung DH, Woodruff J et al. Analysis of prognostic factors in 1,041 patients with localized soft tissue sarcomas of the extremities. J Clin Oncol 1996;14:1679–1689 and Coindre JM, Terrier P, Bui NB et al. Prognostic factors in adult patients with locally controlled soft tissue sarcoma. A study of 546 patients from the French Federation of Cancer Centers Sarcoma Group. J Clin Oncol 1996;14:869–877.

four). This early randomized trial helped establish an interest in the study of adjuvant chemotherapy in soft tissue sarcoma. Other small studies have also suggested a benefit from adjuvant chemotherapy [13, 14]. But, relapse and/or survival benefit from adjuvant chemotherapy was not demonstrated in other trials [15]. The relative infrequency of sarcoma has hampered the ability to accrue a large number of patients with uniform prognostic features to enable the detection of a small but clinically meaningful improvement in survival from adjuvant therapy.

Meta-Analysis of Adjuvant Chemotherapy in Sarcoma

Meta-analyses of multiple studies have been performed and reported in an effort to overcome some of the statistical limitations of trials with small numbers of patients [16, 17]. The Sarcoma Meta-Analysis Collaboration (SMAC) published, in 1997, the finding of a significant benefit from adjuvant doxorubicin-based chemotherapy in time to local and distant recurrence and recurrence free-survival in patients with localized soft tissue sarcoma [18]. Those authors reported a trend toward a higher overall survival rate in patients receiving chemotherapy, with an absolute benefit of 4% (7% for patients with extremity sarcoma) at 10 years, representing a possible survival improvement from 50% to 54% over chemotherapy. Approximately 60% of the patients included in the meta-analysis had sarcoma localized in an extremity. The effort was unique to previous meta-analyses of sarcoma adjuvant therapy in that updated individual patient data from 1,568 participants randomized to adjuvant chemotherapy or no chemotherapy after definitive local control in one of 14 trials was collected from primary trial investigators and combined into a central database for time-to-event analysis. Patients included in the analysis were accrued to trials in the years 1973–1990; the median follow-up was relatively long at 9.4 years, with a range of 5–17 years. The significance of the findings has been criticized because of the inclusion of patients with low-grade and small sarcomas, which may have diluted the benefit from chemotherapy for more high-risk tumors, and lack of information regarding tumor size, grade, and histology in 37%, 28%, and 18% of cases, respectively, despite the attempt to collect primary data. Moreover, the planned dose intensity of doxorubicin administered varied substantially in the trials in the range of 200–550 mg/m^2 and ifosfamide was not part of the treatment regimen.

Pervaiz and colleagues recently expanded the SMAC analysis by including the results of five contemporary randomized controlled studies using an anthracycline and ifosfamide that were not included in the original database [19]. Approximately 95% of the patients in the analysis had sarcoma localized to an extremity or body wall, areas in which complete resection of sarcoma with negative surgical margins is most likely achieved. The update found statistically significant lower local, distant, and overall recurrence rates and longer overall survival for patients receiving adjuvant chemotherapy. The absolute reduction in the risk for recurrence was greater in the five pooled contemporary studies than in the original analysis, and the authors suggested that the effect may be a result of the inclusion of ifosfamide in the adjuvant chemotherapy and/or intensification of the anthracycline dose (Table 2). Analysis of the five trials that, in total, randomized >200 patients to anthracycline and ifosfamide and >200 to no chemotherapy suggests an approximate 10% lower absolute risk for distant recurrence and death for the patients receiving chemotherapy. There was a 30% versus 41% risk for death for patients receiving versus not receiving an anthracycline and ifosfamide, respectively, and a 40% versus 46% risk for death for patients receiving chemotherapy versus no chemotherapy, respectively, in the complete analysis. Data combined from all the trials suggest that 10 and 17 patients would need to be treated with adjuvant chemotherapy to prevent one recur-

Table 2. Risk reductions from meta-analysis of adjuvant chemotherapy in soft tissue sarcoma

	Recurrence			Survival		
Treatment	**RR**	**95% CI**	**ARR**	**RR**	**95% CI**	**ARR**
Doxorubicin	0.69	0.56–0.86	9%	0.84	0.68–1.03	5%
Doxorubicin + ifosfamide	0.61	0.41–0.92	12%	0.56	0.36–0.85	11%

Abbreviations: ARR, absolute risk reduction; CI, confidence interval; RR, relative risk.
Adapted from Pervaiz N, Colterjohn N, Farrokhyar F et al. A systematic meta-analysis of randomized controlled trials of adjuvant chemotherapy for localized resectable soft-tissue sarcoma. Cancer 2008;113:573–581.

rence and one death, respectively, from sarcoma. There are weaknesses of the analysis, which include the use of published aggregate data rather than individual patient data and no attempt to obtain recent follow-up. The planned chemotherapy dose intensity varied among studies in the range of 150–300 mg/m^2 for doxorubicin, 300–600 mg/m^2 for epirubicin, and 15–45 g/m^2 for ifosfamide. Nevertheless, the analysis provides compelling support for the use of adjuvant chemotherapy, notably an anthracycline and ifosfamide, in patients with high-risk localized soft tissue sarcoma involving an extremity or trunk.

The Italian Experience

A detailed discussion of the more recent randomized controlled trials of adjuvant chemotherapy in soft tissue sarcoma is helpful to interpret the meta-analyses. Frustaci and colleagues in Italy performed a randomized trial of five cycles of epirubicin (120 mg/m^2 per cycle) and ifosfamide (9 g/m^2 per cycle) given adjuvantly versus no chemotherapy in 104 patients with high-grade, ≥5 cm, subfascial (American Joint Commission on Cancer [AJCC] stage III) soft tissue sarcoma excised from an extremity or limb girdle [20]. Patients with locally recurrent tumors (18 patients) were eligible regardless of tumor size. Eligible subtypes included fibrosarcoma, malignant fibrous histiocytoma, pleomorphic liposarcoma, leiomyosarcoma, synovial sarcoma, malignant peripheral nerve sheath tumor, pleomorphic rhabdomyosarcoma, and angiosarcoma. Patients were stratified by tumor size (<10 cm versus ≥10 cm) and local recurrence (no versus yes) and randomized after definitive local therapy. Chemotherapy was started at a median interval of 2 months after surgery. In the initial report, the median follow-up was 5 years. An intent-to-treat analysis (though seven patients randomized to chemotherapy did not receive treatment because four withdrew consent and metastases were detected in the other three prior to chemotherapy) detected a trend toward a higher rate of distant relapse-free survival at 2 years, but not at 4 years, and a higher overall survival rate at 4 years (69% survival rate in the chemotherapy arm compared with a 50% survival rate in the control group at 4 years).

An updated analysis of the Italian study after a median follow-up of 90 months revealed a higher 5-year survival rate for patients randomized to adjuvant chemotherapy and a trend toward a longer median overall survival duration [21]. However, excluding the seven patients in the treatment arm who did not receive chemotherapy, 18 of 48 patients had died, whereas 28 of 51 patients in the control group had died, and the difference reached significance defined as $p < .05$. An unplanned subgroup analysis suggested more benefit from chemotherapy for patients who received ≥85% of the planned cumulative dose of chemotherapy than for patients receiving <85% of the planned dose or no chemotherapy. The authors suggested that chemotherapy dose intensity in adjuvant treatment of soft tissue sarcoma may impact results.

Another randomized study of adjuvant epirubicin with or without ifosfamide versus no chemotherapy in consecutive patients with de novo nonmetastatic soft tissue sarcoma was reported, by Petrioli et al. [22], to show a significantly higher 5-year disease-free survival rate with chemotherapy. That trial was not restricted to patients with sarcoma in an extremity, but complete resection was required for study participation. The large majority had malignant fibrous histiocytoma (undifferentiated pleomorphic sarcoma), liposarcoma, or leiomyosarcoma, whereas <10% had another subtype of sarcoma. More patients in the chemotherapy than in the control arm had a sarcoma in an extremity or grade II tumor, which may have biased the results in favor of the chemotherapy arm. However, more of the sarcomas in the control arm were <5 cm, which may have favored the control arm. Approximately 50% of the patients in the trial had tumors <5 cm. Chemotherapy-treated patients received a mean dose of 95% of a planned 300 mg/m^2 (75 mg/m^2 per cycle for four cycles) of epirubicin. Nineteen of 45 patients who received chemotherapy had a mean dose of 95% of a planned 24 g/m^2 (6 g/m^2 per cycle for four cycles) of ifosfamide concurrent with epirubicin. The disease-free

Table 3. Survival rates in patients with high-grade extremity soft tissue sarcoma treated with or without chemotherapy

Study	Sarcoma type	Chemotherapy	Disease-specific survival rate
Eilber et al. (2007) [26]	Synovial sarcoma	Yes	4-yr, 88%
		No	4-yr, 67%
Eilber et al. (2004) [27]	Liposarcoma	Yes	5-yr, 92%
		No	5-yr, 65%
Grobmyer et al. (2004) [25]	≥5 cm[a]	Yes	3-yr, 79%
		No	3-yr, 71%
	>10 cm	Yes	3-yr, 83%
		No	3-yr, 62%
DeLaney et al. (2003) [28]	≥8 cm	Yes	5-yr, 87%[b]
		No	5-yr, 58%[b]

[a]Courtesy of Stephen Grobmyer, M.D., and Elyn Riedel, M.A., Memorial Sloan-Kettering Cancer Center.
[b]Overall survival rate.

and overall survival rates at 5 years for patients receiving chemotherapy were 69% and 72%, respectively, and for those not receiving chemotherapy were 44% and 47%, respectively. For the group of patients accrued to the study after the chemotherapy arm was amended to include ifosfamide, the disease-free and overall survival rates at 5 years for patients receiving chemotherapy were 82% and 84%, respectively, and for those not receiving chemotherapy were 46% and 57%, respectively. Unfortunately, the single-institution trial took >10 years to accrue 88 patients and was closed early because of the poor rate of accrual, and thus was relatively underpowered.

Other Randomized Trials of Doxorubicin and Ifosfamide

Two other published studies of doxorubicin plus ifosfamide as additional therapy for localized soft tissue sarcoma deserve mention. The Austrian Cooperative Soft Tissue Study Group performed a relatively small randomized study of six cycles of adjuvant doxorubicin, ifosfamide, and dacarbazine versus no chemotherapy in 59 patients with resected, localized soft tissue sarcoma [23]. The planned doses of doxorubicin and ifosfamide were 300 mg/m^2 and 36 g/m^2, respectively. Twenty-five of the 31 patients randomized to chemotherapy had a grade 3 tumor, whereas 16 of the 28 patients randomized to the control arm had grade 3 sarcoma, favoring the control arm. After a short mean observation period of 41 months, seven of the 31 patients treated with chemotherapy and 12 of the 28 patients in the control arm suffered sarcoma relapse. The relapse-free survival rate was significantly better in patients with grade 3 sarcomas treated with chemotherapy than in patients treated without chemotherapy. Overall survival was not different between the two arms, but the length of follow-up (mean, 41 months; range, 8–84 months) was likely too short to show a difference.

Gortzak and colleagues reported on a randomized study of preoperative doxorubicin and ifosfamide in patients with "high-risk" sarcomas, suggesting no benefit from chemotherapy over surgery and radiation [24]. High-risk disease was defined as sarcoma >8 cm of any grade and grade 2 or 3 sarcoma <8 cm locally recurrent or inadequately excised. One hundred fifty patients were randomized and 134 were eligible. The treatment arms were well balanced regarding tumor size, location, and grade. Sarcoma was low grade in 8%. The objective response rate to preoperative treatment was 28%. After a median follow-up interval >7 years, the time to relapse and survival rates between the arms were similar. Chemotherapy was limited to three cycles, resulting in a planned cumulative doxorubicin dose of 150 mg/m^2 and ifosfamide dose of 15 g/m^2, which are substantially lower than doses used in adjuvant studies; thus, dose intensity in this neoadjuvant trial could be considered inadequate for systemic therapy.

Nonrandomized Institutional Experience with Adjuvant Chemotherapy for Soft Tissue Sarcoma

An analysis of patients with ≥5 cm, high-grade, deep soft tissue sarcoma localized to an extremity treated at Memorial Sloan-Kettering Cancer Center or Dana-Farber Cancer Institute suggested that adjuvant chemotherapy with doxorubicin and ifosfamide resulted in longer disease-specific survival (Table 3) [25]. Patients were selected from prospectively maintained databases at the institutions and outcomes of patients treated without or with chemotherapy

were compared. Seventy-four patients received a mean of three cycles of doxorubicin (75 mg/m^2) and ifosfamide (6–9 g/m^2) chemotherapy and 282 were treated without chemotherapy. Even though patients were not randomized to treatment, the groups were reasonably well balanced in tumor site (upper versus lower extremity), histology (except for synovial sarcoma), margin status, and follow-up interval. Patients treated with chemotherapy tended to be younger and have larger tumors than patients not receiving chemotherapy. The median follow-up at the time of the analysis was about 3 years. The disease-specific survival rate in patients treated with chemotherapy was better than that in patients treated without chemotherapy (the hazard ratio for effect of chemotherapy on survival was 0.52, a relative difference of about 50%). The beneficial effect of chemotherapy seemed to be most pronounced in patients with sarcoma >10 cm in size and seemed to be driven by a lower risk for distant metastasis in the chemotherapy-treated than in the control population. Patients with larger sarcomas receiving chemotherapy had a 21% absolute survival benefit at 3 years, compared with patients not receiving chemotherapy.

An analysis of patients with >5 cm, deep synovial sarcoma localized to an extremity treated without or with chemotherapy at Memorial Sloan-Kettering Cancer Center or the University of California, Los Angeles, showed lower rates of distant recurrence and death from synovial sarcoma for patients receiving doxorubicin and ifosfamide chemotherapy in addition to local treatment than for patients receiving local therapy alone [26]. Similar to the analysis discussed in the preceding paragraph, patient cases were culled from prospectively maintained databases at the institutions. Chemotherapy using doxorubicin and ifosfamide ($n = 31$), doxorubicin, ifosfamide, and cisplatin ($n = 25$), or doxorubicin, ifosfamide, and dacarbazine ($n = 12$) was administered to 68 patients and no chemotherapy was administered to 38 patients. Patients treated with chemotherapy received a median of four cycles and a relatively high median dose of ifosfamide of 12 g/m^2 per cycle. The treatment groups were well matched for patient age, tumor size, histologic subtype, surgical procedure, and use of radiation. More of the patients who did not receive chemotherapy had microscopic positive surgical margins, but there was no difference in the local relapse rate between the groups. The duration of follow-up for surviving patients was longer in the control group. A multivariate analysis demonstrated that tumor size and the use of chemotherapy were independently associated with sarcoma-specific survival. The disease-specific survival rate at 4 years was 88% for the patients receiving chemotherapy, compared with 67% for the patients not receiving chemotherapy, a 21% greater absolute survival rate in the chemotherapy-treated group.

Patients with >5 cm, high-grade liposarcoma confined to an extremity treated at Memorial Sloan-Kettering Cancer Center or the University of California, Los Angeles, with doxorubicin and ifosfamide were also shown to have a lower risk for death from sarcoma than a contemporary cohort of patients treated without chemotherapy [27]. The groups were balanced for histologic subtype (e.g., myxoid/round cell, pleomorphic, and dedifferentiated). Patients receiving chemotherapy were younger and more likely to have negative microscopic surgical margins. The median follow-up interval was longer in the chemotherapy-treated group. Multivariate analysis revealed that treatment using chemotherapy, smaller tumor size, and myxoid/round cell subtype were independently associated with longer survival. The 5-year sarcoma-specific survival rates for patients receiving versus not receiving chemotherapy were 92% and 65%, respectively, an absolute difference >25%.

DeLaney and colleagues at Massachusetts General Hospital prospectively studied outcomes in patients with ≥8 cm, high-grade soft tissue sarcoma confined to an extremity treated with doxorubicin, ifosfamide, and dacarbazine for six cycles, radiation, and complete resection [28]. The first three chemotherapy cycles were interdigitated with radiation. More than 80% of the 48 patients studied were able to complete six cycles of chemotherapy. Outcome was compared with that of a contemporary cohort of patients matched for tumor size, tumor grade, and patient age who did not receive the protocol chemoradiotherapy. The rate of local relapse was similar between groups, but the distant relapse-free and survival rates were significantly better in the group treated with chemoradiotherapy. The rates of disease-free and overall survival at 5 years for patients receiving the chemoradiation protocol versus the matched control group were 70% versus 42% and 87% versus 58%, respectively. Further study of the chemoradiotherapy protocol in a broader cooperative group platform resulted in fewer patients completing the prescribed chemotherapy, more toxicity, and inferior outcomes [29]. The Massachusetts General Hospital study was conducted by a multidisciplinary group of sarcoma specialists at one institution, whereas the cooperative group study enrolled 66 patients from 30 institutions. The poorer results from this regimen in the cooperative group setting suggest that specialized experience with a complicated and potentially toxic treatment protocol significantly affects outcome.

Cormier and colleagues performed a retrospective analysis that seems to refute the advantage from adjuvant chemotherapy seen in the studies discussed above. They reviewed the experience of 674 consecutive patients with AJCC stage III extremity soft tissue sarcoma treated at the MD Anderson Cancer Center and Memorial Sloan-Ketter-

ing Cancer Center during a 15-year period and did not find a sustained benefit from adjuvant chemotherapy [30]. The nonrandomized comparison was balanced for tumor size, patient sex, and quality of the surgical margin of the resected sarcoma, but there were more patients in the chemotherapy-treated group with "other" sarcomas (not undifferentiated pleomorphic sarcoma/malignant fibrous histiocytoma, liposarcoma, leiomyosarcoma, synovial sarcoma, and undifferentiated sarcoma) and there were more patients with liposarcoma in the "control" group, which may have favored the group not treated with chemotherapy. Overall, 18% of the patients had an "other" sarcoma histopathologic subtype. All the patients received doxorubicin, but the dose intensity of the chemotherapy and the percentage of patients receiving ifosfamide were not reported. The median follow-up for surviving patients was 6 years and the disease-specific survival rate at 5 years was 61%. Analysis showed that the disease-specific survival rate was higher during the first year for patients treated with chemotherapy but was no different than for the control group at 5 years. In this nonrandomized comparison, different selection bias by the institutions occurred, with a majority of patients at the MD Anderson Cancer Center and a minority of patients at Memorial Sloan Kettering Cancer Center receiving chemotherapy (MD Anderson patients not receiving chemotherapy may have had a favorable prognosis and Memorial Sloan-Kettering patients treated with chemotherapy may have had a poor prognosis). The authors noted that comparisons of the subgroup of patients who survived >1 year should be interpreted with caution because deaths occurring during the first year may have significantly unbalanced the groups. The retrospective nature of the analysis does not allow conclusions about the mechanisms underlying the time-varying effects of chemotherapy in this study to be drawn.

Neoadjuvant Chemotherapy in Soft Tissue Sarcoma

Neoadjuvant chemotherapy in the treatment of localized soft tissue sarcoma has been undertaken to assess sarcoma response to therapy, initiate early treatment of microscopic tumor metastasis, and improve local outcomes from surgery, but only a few studies have analyzed relapse-free and survival rates by primary tumor response. A complete or near complete (>95%) pathologic sarcoma response to preoperative chemotherapy and radiation, seen in about half of the population studied, was independently associated with lower local recurrence and better survival rates in patients with extremity, high-grade soft tissue sarcoma [31]. The 5- and 10-year survival rates for patients with a favorable pathologic tumor response to preoperative therapy were 80% and 71%, respectively, compared with 62% and 55%, respectively, in patients with a poorer tumor response. Changes in extremity soft tissue sarcoma fluorodeoxyglucose (FDG) uptake after preoperative chemotherapy may also be predictive of long-term outcome. Patients with a substantial decline in sarcoma FDG uptake measured by positron emission tomography after chemotherapy had a significantly lower risk for sarcoma recurrence and longer survival than patients with little to no change in FDG uptake [32]. The approximate 5-year recurrence-free and overall survival rates for patients with a large decline in tumor FDG uptake were 80% and 75%, respectively, compared with 35% and 35%, respectively, for patients with no significant change in FDG uptake with chemotherapy. The relative risk for dying from sarcoma was four times greater in the group without than in the group with a sarcoma response to doxorubicin-based chemotherapy. Patients with evidence of radiographic or pathologic response of localized soft tissue sarcoma to chemotherapy combined with regional hyperthermia also had a significantly higher survival rate than patients without a tumor response to preoperative therapy [33]. Collectively, the reports suggest that patients with localized soft tissue sarcoma that respond to chemotherapy with or without radiation seem to have a lower risk for relapse and longer survival as a direct effect of chemotherapy on undetected microscopic metastases. An alternative hypothesis that tumor response to preoperative therapy is only a prognostic marker for a lower risk for tumor metastasis seems less plausible.

Adjuvant Chemotherapy for Cancer

The use of adjuvant chemotherapy is an established standard practice for osteosarcoma, Ewing's family of tumors, and the pediatric rhabdomyosarcomas because of demonstrably higher disease-free and overall survival rates in randomized studies. Adjuvant chemotherapy in the management of localized, high-grade osteosarcoma was shown to reduce relapse rates by >50% (from 80%–90% without chemotherapy to 35%–45% with chemotherapy at 2 years) and significantly improve survival to a substantial degree [34, 35]. Because of the large difference in outcomes, a significant benefit from adjuvant treatment was detected in the very small study of 36 patients by Link et al. [35]. The addition of doxorubicin to a regimen of cyclophosphamide, dactinomycin, and vincristine as adjuvant chemotherapy for patients with localized Ewing's sarcoma resulted in a significantly higher 5-year survival rate, 60% versus 24%, in a randomized trial of 222 patients, and thus became a standard component of Ewing's chemotherapy [36]. The significant difference in outcomes between the groups (chemotherapy versus no chemotherapy, doxorubicin versus no

doxorubicin) could be readily demonstrated in relatively small studies because of the large magnitude of the chemotherapy effect. More recently, the addition of ifosfamide and etoposide to the standard chemotherapy backbone for the treatment of patients with localized Ewing's sarcoma was shown to lead to a greater 5-year event-free survival rate, 69% versus 54%, and greater overall survival rate, 72% versus 61% (an absolute difference of about 10%) [37]. This more modest gain in survival was significant but required a 400-patient trial based on the underlying pre-study assumption that addition of ifosfamide and etoposide would halve the failure rate within 3 years of follow-up.

Adjuvant chemotherapy is often employed in the management of epithelial cancer for, at times, relatively small gains in disease-free and overall survival. For example, in women >50 years of age with estrogen receptor–negative breast cancer, adjuvant chemotherapy reduces the risk for recurrence and death at 10 years by about 10% and 6%, respectively [38]. This modest improvement in survival is felt to be clinically relevant and justify the 1%–2% risk for treatment-related mortality by the National Comprehensive Cancer Network Breast Cancer Committee, which recommends the use of adjuvant chemotherapy in the management of patients with estrogen receptor–negative, node-negative invasive breast cancer >5 mm [39]. The statistical significance of small improvements in survival with chemotherapy in breast cancer studies is aided by the inclusion of large numbers of patients. In the meta-analysis of adjuvant chemotherapy in estrogen receptor–poor breast cancer, data from approximately 6,000 randomized patients were analyzed [38]. The risk reduction in breast cancer patients from adjuvant therapy of relatively small (5–20 mm) tumors is similar to the risk reduction for sarcoma relapse and death from adjuvant therapy in the sarcoma meta-analysis. A multithousand patient randomized trial of adjuvant chemotherapy in high-grade, primary soft tissue sarcoma is not likely to be conducted, even with multinational collaboration, because of the infrequency of the disease. The SMAC suggested that a randomized trial of approximately 900 patients would be required to detect a 10% difference in overall survival with adjuvant chemotherapy; a trial to detect a 6% difference, as seen in small, estrogen receptor–negative breast cancer, would require far in excess of 1,000 patients. The magnitude of benefit from adjuvant chemotherapy in unselected soft tissue sarcoma is likely to be relatively small, and large-scale randomized trials of adjuvant chemotherapy in soft tissue sarcoma are unlikely to be performed; therefore, "level 1" evidence to support or refute the use of adjuvant chemotherapy is not likely to be available. Recommendations for the use of adjuvant chemotherapy in localized soft tissue sarcoma should consider the risk for disease relapse to the patient, the sarcoma histologic subtype, and the available evidence from meta-analyses, small randomized studies, and analyses of data from prospectively maintained institutional databases.

Conclusions

Taking into account the facts discussed above and the negative trials described in the companion manuscript by Drs. Blay and Le Cesne [40], the answer to the question posed in the opening statement of this manuscript is "yes." We strongly feel that there is "reasonable" evidence to support the use of more contemporary chemotherapy in selected patients with high-risk localized soft tissue sarcomas. While we all anxiously await molecularly targeted therapy with a much better therapeutic index, it is our obligation to use the currently available agents to the best of our ability to help patients who are presently in our clinics. So how should the decision making proceed in the clinic? In our opinion, patients with high-risk disease, defined as >5 cm, high-grade, and deep soft tissue sarcomas, regardless of location, should be considered for adjuvant, or preferably neoadjuvant, systemic therapy. Patients who are generally healthy, physiologically ≤65 years of age, with intact organ function, including two functioning kidneys, should be considered for a dose-intensive anthracycline and ifosfamide combination with growth factor support. Individuals who are older or have comorbidities resulting in a compromise of performance status or organ function may still benefit from anthracycline-based regimens, as shown by the SMAC data. In selecting patients for adjuvant therapy, one also needs to consider histologic subtypes. Those that have historically been known to be resistant or poorly sensitive to conventional agents (alveolar soft-part sarcomas, clear cell sarcomas, hemangiopericytomas, extraskeletal myxoid chondrosarcomas, epithelioid sarcomas, etc.) should be excluded, and those patients should be spared the unnecessary toxicities of the regimen. Although such an approach has been criticized in the past for patient selection, we would submit that this in fact represents good clinical judgment—something we all are trained in and should use in day-to-day routine practice. The lessons learned from historic gastrointestinal leiomyosarcomas being insensitive to conventional chemotherapeutic agents yet always included in large randomized trials to be "inclusive" and now the clear recognition that this is a unique entity redefined as gastrointestinal stromal tumor should serve as the basis for personalizing therapy. This complex group of diverse diseases that, for simplicity, we identify as soft tissue sarcomas certainly is not one uniform disease entity. As for the question of the preoperative versus postoperative use of adjuvant chemotherapy, again, lessons learned from the osteosarcoma experience teach us that when chemotherapy is indicated and planned, it makes infinitely greater sense to use it with disease in place to serve as a marker and an in vivo test of the efficacy of the toxic and marginally effective chemotherapy.

So, in conclusion, acknowledging the data, the variable interpretation, and personal physician bias on both sides of the aisle as outlined in these companion manuscripts, added to the irrefutable fact that an appropriately powered, randomized, adjuvant therapy trial in uniform subsets of patients with currently available agents is unlikely to happen, we should use the available agents and information to best serve the patients for which we care. We therefore recommend that systemic therapy with an anthracycline or anthracycline and ifosfamide combination should be considered, preferably preoperatively, in appropriately selected patients with soft tissue sarcoma that are at a high risk for recurrence and/or metastases. Such interventions are always preferable in clinical trials attempting to either improve efficacy or attenuate toxicities or both. With recent advances in molecular biology resulting in the identification of specific targets and in light of the classic and enviable example of imatinib in gastrointestinal stromal tumor, we remain quite optimistic that significant progress is likely to be made in the foreseeable future and hope that new treatments may well make this current debate moot.

Author Contributions

Conception/Design: Scott M. Schuetze, Shreyaskumar Patel
Financial support: Scott M. Schuetze, Shreyaskumar Patel
Data analysis and interpretation: Scott M. Schuetze, Shreyaskumar Patel
Manuscript writing: Scott M. Schuetze, Shreyaskumar Patel
Final approval of manuscript: Scott M. Schuetze, Shreyaskumar Patel

References

1 Fletcher CDM, Unni KK, Mertens F, eds. Pathology and Genetics of Tumours of Soft Tissue and Bone. Lyon, France: IARC Press, 2002:427.

2 Bhangu AA, Beard JA, Grimer RJ. Should soft tissue sarcomas be treated at a specialist centre? Sarcoma 2004;8:1–6.

3 Jemal A, Siegel R, Ward E et al. Cancer statistics, 2009. CA Cancer J Clin 2009;59:225–249.

4 Reis LAG, Harkins D, Krapcho M et al. SEER Cancer Statistics Review, 1975–2004. Bethesda, MD: National Cancer Institute, 2007. Available at http://seer.cancer.gov/csr/1975_2004/, accessed December 31, 2008.

5 Coindre JM, Terrier P, Bui NB et al. Prognostic factors in adult patients with locally controlled soft tissue sarcoma. A study of 546 patients from the French Federation of Cancer Centers Sarcoma Group. J Clin Oncol 1996;14:869–877.

6 Pisters PW, Leung DH, Woodruff J et al. Analysis of prognostic factors in 1,041 patients with localized soft tissue sarcomas of the extremities. J Clin Oncol 1996;14:1679–1689.

7 Stefanovski PD, Bidoli E, De Paoli A et al. Prognostic factors in soft tissue sarcomas: A study of 395 patients. Eur J Surg Oncol 2002;28:153–164.

8 Weitz J, Antonescu CR, Brennan MF. Localized extremity soft tissue sarcoma: Improved knowledge with unchanged survival over time. J Clin Oncol 2003;21:2719–2725.

9 Benjamin RS, Wiernik PH, Bachur NR. Adriamycin: A new effective agent in the therapy of disseminated sarcomas. Med Pediatr Oncol 1975;1:63–76.

10 O'Bryan RM, Luce JK, Talley RW et al. Phase II evaluation of adriamycin in human neoplasia. Cancer 1973;32:1–8.

11 Edmonson JH, Ryan LM, Blum RH et al. Randomized comparison of doxorubicin alone versus ifosfamide plus doxorubicin or mitomycin, doxorubicin, and cisplatin against advanced soft tissue sarcomas. J Clin Oncol 1993;11:1269–1275.

12 Rosenberg SA, Tepper J, Glatstein E et al. Prospective randomized evaluation of adjuvant chemotherapy in adults with soft tissue sarcomas of the extremities. Cancer 1983;52:424–434.

13 Gherlinzoni F, Bacci G, Picci P et al. A randomized trial for the treatment of high-grade soft-tissue sarcomas of the extremities: Preliminary observations. J Clin Oncol 1986;4:552–558.

14 Ravaud A, Bui BN, Coindre J et al. Adjuvant chemotherapy with cyvadic in high risk soft tissue sarcoma: A randomized prospective trial. In: Salmon SE, ed. Adjuvant Therapy of Cancer, Volume VI. Philadelphia: WB Saunders, 1990:556–566.

15 Antman K, Suit H, Amato D et al. Preliminary results of a randomized trial of adjuvant doxorubicin for sarcomas: Lack of apparent difference between treatment groups. J Clin Oncol 1984;2:601–608.

16 Tierney JF, Mosseri V, Stewart LA et al. Adjuvant chemotherapy for soft-tissue sarcoma: Review and meta-analysis of the published results of randomised clinical trials. Br J Cancer 1995;72:469–475.

17 Zalupski MM, Ryan JR, Hussein ME et al. Defining the role of adjuvant chemotherapy for patients with soft tissue sarcoma of the extremities. In: Salmon SE, ed. Adjuvant Therapy of Cancer, Volume VII. Philadelphia: JB Lippincott, 1993:385–392.

18 Adjuvant chemotherapy for localised resectable soft-tissue sarcoma of adults: Meta-analysis of individual data. Sarcoma Meta-Analysis Collaboration. Lancet 1997;350:1647–1654.

19 Pervaiz N, Colterjohn N, Farrokhyar F et al. A systematic meta-analysis of randomized controlled trials of adjuvant chemotherapy for localized resectable soft-tissue sarcoma. Cancer 2008;113:573–581.

20 Frustaci S, Gherlinzoni F, De Paoli A et al. Adjuvant chemotherapy for adult soft tissue sarcomas of the extremities and girdles: Results of the Italian randomized cooperative trial. J Clin Oncol 2001;19:1238–1247.

21 Frustaci S, De Paoli A, Bidoli E et al. Ifosfamide in the adjuvant therapy of soft tissue sarcomas. Oncology 2003;65(suppl 2):80–84.

22 Petrioli R, Coratti A, Correale P et al. Adjuvant epirubicin with or without ifosfamide for adult soft-tissue sarcoma. Am J Clin Oncol 2002;25:468–473.

23 Brodowicz T, Schwameis E, Widder J et al. Intensified adjuvant IFADIC chemotherapy for adult soft tissue sarcoma: A prospective randomized feasibility trial. Sarcoma 2000;4:151–160.

24 Gortzak E, Azzarelli A, Buesa J et al. A randomised phase II study on neoadjuvant chemotherapy for 'high-risk' adult soft-tissue sarcoma. Eur J Cancer 2001;37:1096–1103.

25 Grobmyer SR, Maki RG, Demetri GD et al. Neo-adjuvant chemotherapy for primary high-grade extremity soft tissue sarcoma. Ann Oncol 2004;15:1667–1672.

26 Eilber FC, Brennan MF, Eilber FR et al. Chemotherapy is associated with improved survival in adult patients with primary extremity synovial sarcoma. Ann Surg 2007;246:105–113.

27 Eilber FC, Eilber FR, Eckardt J et al. The impact of chemotherapy on the survival of patients with high-grade primary extremity liposarcoma. Ann Surg 2004;240:686–695; discussion 695–697.

28 DeLaney TF, Spiro IJ, Suit HD et al. Neoadjuvant chemotherapy and radiotherapy for large extremity soft-tissue sarcomas. Int J Radiat Oncol Biol Phys 2003;56:1117–1127.

29 Kraybill WG, Harris J, Spiro IJ et al. Phase II study of neoadjuvant chemo-

therapy and radiation therapy in the management of high-risk, high-grade, soft tissue sarcomas of the extremities and body wall: Radiation Therapy Oncology Group Trial 9514. J Clin Oncol 2006;24:619–625.

30 Cormier JN, Huang X, Xing Y et al. Cohort analysis of patients with localized, high-risk, extremity soft tissue sarcoma treated at two cancer centers: Chemotherapy-associated outcomes. J Clin Oncol 2004;22:4567–4574.

31 Eilber FC, Rosen G, Eckardt J et al. Treatment-induced pathologic necrosis: A predictor of local recurrence and survival in patients receiving neoadjuvant therapy for high-grade extremity soft tissue sarcomas. J Clin Oncol 2001;19:3203–3209.

32 Schuetze SM, Rubin BP, Vernon C et al. Use of positron emission tomography in localized extremity soft tissue sarcoma treated with neoadjuvant chemotherapy. Cancer 2005;103:339–348.

33 Issels RD, Abdel-Rahman S, Wendtner C et al. Neoadjuvant chemotherapy combined with regional hyperthermia (RHT) for locally advanced primary or recurrent high-risk adult soft-tissue sarcomas (STS) of adults: Long-term results of a phase II study. Eur J Cancer 2001;37:1599–1608.

34 Eilber F, Giuliano A, Eckardt J et al. Adjuvant chemotherapy for osteosarcoma: A randomized prospective trial. J Clin Oncol 1987;5:21–26.

35 Link MP, Goorin AM, Miser AW et al. The effect of adjuvant chemotherapy on relapse-free survival in patients with osteosarcoma of the extremity. N Engl J Med 1986;314:1600–1606.

36 Nesbit ME Jr, Gehan EA, Burgert EO Jr et al. Multimodal therapy for the management of primary, nonmetastatic Ewing's sarcoma of bone: A long-term follow-up of the First Intergroup study. J Clin Oncol 1990;8:1664–1674.

37 Grier HE, Krailo MD, Tarbell NJ 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.

38 Early Breast Cancer Trialists' Collaborative Group (EBCTCG); Clarke M, Coates AS, Darby SC et al. Adjuvant chemotherapy in oestrogen-receptor-poor breast cancer: Patient-level meta-analysis of randomised trials. Lancet 2008;371:29–40.

39 Carlson RW, McCormick B. Update: NCCN breast cancer clinical practice guidelines. J Natl Compr Canc Netw 2005;3(suppl 1):S7–S11.

40 Blay JY, Le Cesne A. Adjuvant chemotherapy in localized soft tissue sarcomas: Still not proven. ***The Oncologist*** 2009;14:1013–1020.