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Sarcoma (SH Okuno, Section Editor)

Preoperative Therapy for Extremity Soft Tissue Sarcomas

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Opinion statement

High-risk soft tissue sarcomas (STS) are defined as large (>5 cm), intermediate/high-grade tumors and can carry a >50 % risk of death from metastases. A regimen of preoperative chemoradiation immediately addresses issues of both local control and micrometastases and should be considered for patients with high-risk STS of the extremities. While acute wound healing complications are more likely to occur, these are most always manageable and reversible, as opposed to the long-term complications associated with higher radiation doses and larger fields required for post-operative therapy. Preoperative treatment also yields potential prognostic information from pathologic treatment response, and quantitative imaging methods hold promise to detect early treatment effect. Definitive evidence of survival benefit from neoadjuvant therapy has been elusive, but a large body of experience has accumulated at dedicated centers where this approach is utilized. Whenever possible, it is imperative that patients with high-risk STS be enrolled on well-designed clinical trials. Treatment planning and administration requires a coordinated multidisciplinary approach that should be undertaken in high-volume centers with expertise in the management of sarcomas.

Introduction

Soft tissue sarcomas (STS) are a rare, heterogeneous group of tumors of mesenchymal origin that account for less than 1 % of all cancers [1]. The upper and lower extremities are the most common site of STS, and historically, the mainstay of treatment was amputation. Current limb-sparing approaches combine wide surgical resection with radiation, resulting in local control rates over 90 % [2–5]. Multiple risk factors for soft tissue sarcoma metastases have been identified, and the highest risk tumors are those that are >5 cm in size with

intermediate or high-grade histology [6]. Despite low rates of local recurrence, approximately 50 % of patients with high-risk STS of the extremity will die from metastatic disease [7]. Systemic treatment with chemotherapy to attempt to eradicate micrometastatic disease is often employed, although results of adjuvant chemotherapy trials have been mixed. The optimal management of these high-risk extremity tumors remains controversial [6, 8••, 9, 10].

Treatment

Radiotherapy

The addition of radiation to standard surgical treatment of extremity STS has allowed for limb-salvage procedures to become the norm rather than the exception. Preference for the use of pre- versus post-operative radiation remains highly institution dependent and results in equivalent local control rates. In general, preoperative radiotherapy is associated with more acute wound complications, but post-operative radiation increases long-term morbidity, including less fibrosis and better functional outcomes (Fig. 1) [11–13, 14••]. We favor the use of preoperative radiation in most patients, given that wound complications are most often manageable and have minimal long-term sequelae, but this is a patient-specific decision that must be made in the context of multidisciplinary discussion at an experienced sarcoma center.

Pharmacologic treatment

Doxorubicin and ifosfamide

Doxorubicin and ifosfamide have been repeatedly shown to be the two most active chemotherapy agents in the treatment of soft tissue sarcoma in the metastatic setting [15–19]. The effectiveness of chemotherapy within individual subtypes has not been well defined, but special consideration should be given to sarcomas thought to be more chemotherapy sensitive, such as synovial sarcoma and myxoid liposarcoma. Theoretically, the addition of systemic therapy to treatment of high-risk patients prior to the development of overt metastases should decrease the rate of distant disease and improve overall survival. However, the results of trials of chemotherapy as an adjunct to surgery and radiation have been mixed, and thus, the use of chemotherapy in localized soft tissue sarcoma remains controversial [6, 8••, 9].

- In 1997, the Sarcoma Meta-Analysis Collaboration (SMAC) analyzed 14 randomized trials of adjuvant doxorubicin-based chemotherapy in over 1500 patients with localized, resectable STS. The meta-analysis demonstrated a statistically significant disease-free survival benefit for treated patients (hazard ratio 0.75, 95 % CI 0.64–0.87, p=0.0001) but no significant overall survival benefit [6]. However, subset analyses suggested that patients with extremity STS had a statistically significant overall survival benefit if treated with adjuvant chemotherapy, equivalent to a 7 % absolute benefit at 10 years.
- In the 2008 SMAC update, four additional trials were analyzed including a total of 1929 patients [10]. Notably, the

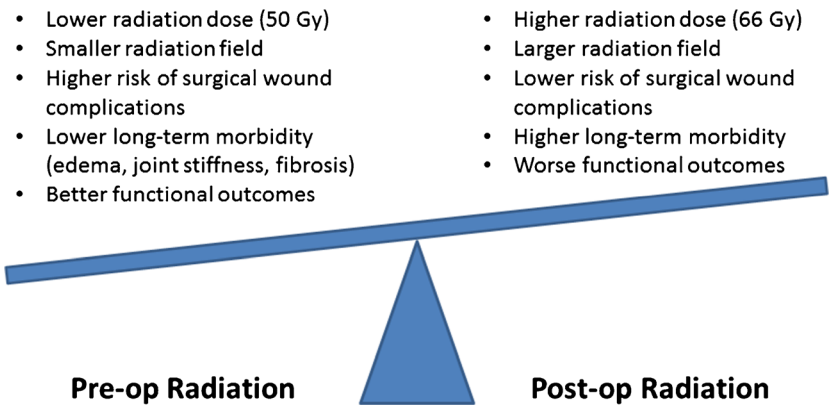

Fig. 1. The benefits of preoperative radiation generally outweigh the risks.

combination of doxorubicin and ifosfamide was included in five of these studies (n=414), and this regimen was associated with a significant reduction in mortality (HR 0.56, 95 % CI 0.36–0.86, p=0.01, NNT=17).

Most randomized trials to date have investigated the role of post-operative chemotherapy, and relatively few preoperative trials have been reported:

- Gortzak et al. produced one of the first publications on a randomized trial of neoadjuvant chemotherapy (n=134) [20]. Doxorubicin and ifosfamide were administered in three 21-day cycles preoperatively. No preoperative radiation was given and post-operative radiation was not routinely given. There was no difference in 5-year disease-free or overall survival, although the study was underpowered.
- A larger, multi-institutional cohort was included in a retrospective analysis by Grobmyer et al. (n=356) [21]. Radiation status was not analyzed. For patients with very large (>10 cm), high-grade tumors, the 3-year disease-specific survival was significantly improved for patients receiving neoadjuvant doxorubicin, ifosfamide, and mesna (AIM; 83 vs. 62 %, p=0.02).

Chemoradiotherapy

The combination of preoperative (neoadjuvant) chemotherapy and radiation has a significant rationale for the management of high-risk extremity STS. In addition to early treatment of micrometastatic disease, radiation-sensitizing preoperative chemotherapy may further decrease the chance of local recurrence.

Large, randomized trials are limited in sarcoma clinical research, and to date, there is no level 1 evidence regarding neoadjuvant chemoradiation. However, a number of institutions have published single-arm studies or retrospective analyses using this approach (Table 1).

- One of the earliest reports was published by Eilber et al. in 1984 and used intra-arterial doxorubicin followed by radiation [22].

Table 1. Published reports of neoadjuvant chemoradiotherapy for soft tissue sarcomas

Report Author	Year	*n*	Chemotherapy Agents	Schedule	Radiation cGy
Eilber [22] (UCLA)	1984	100	Doxorubicin (intra-arterial)	Continuous 3-day infusion	3500
Eilber [23] (UCLA)	1995	61	Doxorubicin Cisplatin Ifosfamide	Ifosfamide×two pre-op cycles and dox/cis×one post-op cycle	2800
Edmonson [24] (Mayo)	2002	39	Doxorubicin Cisplatin Ifosfamide Mitomycin	Three pre-op 28-day cycles	4500 (plus additional 1000–2000 post-op)
Delaney [25] and Mullen [26••] (MGH)	2003, 2012	48	Doxorubicin Ifosfamide Dacarbazine	Three pre-op 21-day cycles and three post-op 21-day cycles	4400
Pisters [27] (MD Anderson)	2004	27	Doxorubicin	Weekly 4-day CIVI for 5 weeks pre-op	5000
Mack [28] (Calgary)	2005	75	Doxorubicin	3 days	3000
Ryan [29] (OHSU)	2008	25	Epirubicin Ifosfamide	Three pre-op 21-day cycles and three post-op 21-day cycles	2800
Kraybill [30] (RTOG 9514)	2010	66	Doxorubicin Ifosfamide Dacarbazine	Three pre-op 21-day cycles and three post-op 21-day cycles	4400
Hong [31] (MGH)	2012	66	Doxorubicin Ifosfamide Dacarbazine	Three pre-op 21-day cycles and three post-op 21-day cycles	4400
Meyer [32•] (OHSU)	2013	18	Epirubicin Ifosfamide Sorafenib	Three pre-op 21-day cycles and three post-op 21-day cycles; sorafenib continuous	2800
Bedi [33] (MCW)	2013	49	Doxorubicin Ifosfamide	Variable regimens	5000 (median)
Raval [34] (Johns Hopkins)	2014	16	Doxorubicin Ifosfamide Dacarbazine	Three pre-op 21-day cycles and three post-op 21-day cycles	4400
Canter [35] (UC Davis)	2014	8	Sorafenib	Continuous pre-op	5000
Lewin [36] (Australia)	2014	7	Sunitinib	Continuous pre-op	5040
Okuno [37] (Mayo)	2014	39	Doxorubicin Ifosfamide Mitomycin Cisplatin	Four 28-day pre-op cycles	4500

Table 1. (Continued)

Report Author	Radiation Schedule	Outcomes Local recurrence (%)	Time point (years)	Overall survival (%)	Time point (years)
Eilber [23] (UCLA)	8 fractions concurrent	2	NR	85	NR
Edmonson [24] (Mayo)	25 fractions concurrent	10	5	80	5
Delaney [25] and Mullen [26••] (MGH)	22 fractions concurrent	8	5	87	5
				66	10
Pisters [27] (MD Anderson)	25 fractions concurrent	NR		NR	
Mack [28] (Calgary)	10 fractions concurrent	3	5	63	5
Ryan [29] (OHSU)	8 fractions concurrent	NR		84	2
Kraybill [30] (RTOG 9514)	22 fractions interdigitated	22	5	71	5
Hong [31] (MGH)	22 fractions interdigitated	9	5	86	5
Meyer [32•] (OHSU)	8 fractions concurrent	0	2	100	2
Bedi [33] (MCW)	25 fractions pre-op	3	3	86	3
Raval [34] (Johns Hopkins)	22 fractions interdigitated	0	3	73	3
Canter [35] (UC Davis)	25 fractions concurrent	NR		NR	
Lewin [36] (Australia)	28 fractions concurrent	NR		56	2
Okuno [37] (Mayo)	25 fractions concurrent	NR		82	3

CIVI continuous IV infusion, *NR* not reported

- Multiple other reports using a similar approach were subsequently reported, but the cumbersome nature of intra-arterial chemotherapy was eventually questioned [23, 38–44].
- The Eilber group at UCLA conducted sequential, non-randomized trials over two decades in which consecutive patients were treated on protocol [23]. These trials used a rapid fractionation radiation scheme in combination with chemotherapy, finding that intravenous chemotherapy results in outcomes similar to those with intra-arterial therapy.

Multi-agent chemotherapy regimens—generally anthracycline and ifosfamide combinations—have been integrated into the most recent neoadjuvant trials:

- DeLaney et al. reported on a pilot study from Massachusetts General Hospital (MGH) of 48 patients who received neoadjuvant MAID chemotherapy (mesna, doxorubicin, ifosfamide, dacarbazine) and "interdigitated" radiotherapy for large (>8 cm), high-grade extremity soft tissue sarcomas [25]. Preoperative treatment consisted of three cycles of MAID with two radiation courses of 11 fractions each to a total of 4400 cGy. Three additional cycles of MAID were given post-operatively. Toxicities included febrile neutropenia (25 %), moist desquamation (29 %), and wound healing complications (29 %). One patient developed myelodysplasia as a late complication. Compared to historical controls, 5-year outcomes were favorable, including disease-free survival (DFS) 70 vs. 42 % (p=0.0002) and overall survival (OS) 87 vs. 58 % (p=0.0003). The inferred survival benefit was sustained, with long-term follow-up data indicating a 10-year OS rate of 66 % compared to 38 % in the historical control cohort (p=0.003) [26••].
- RTOG 9514 was a multi-institutional trial mirroring the treatment plan outlined by DeLaney et al. and enrolled 66 high-risk STS patients [30]. Unfortunately, the regimen resulted in excessive toxicity: 97 % of patients experienced grade 3 or higher toxicity, including three treatment-related deaths. Therefore, the applicability of such a complicated neoadjuvant protocol outside of a dedicated sarcoma center is questionable. Nonetheless, 5-year outcomes of DFS 56 % and OS 71 % are notable.
- Our center has investigated the use of another chemoradiotherapy regimen employing rapid fractionation radiation per the UCLA experience and administering epirubicin and ifosfamide, based on the regimen used by the randomized Italian adjuvant trial reported by Frustaci et al. in 2001 [29, 45]. Twenty-five patients with high-risk soft tissue sarcomas of the extremity or body wall were enrolled. Three pre- and three post-operative cycles of epirubicin and ifosfamide were administered, with omission of epirubicin during the second cycle while 2800 cGy radiotherapy administered in eight fractions [44]. Two-year DFS and OS were 62 and 84 %, respectively. Toxicities were significant, with 84 % experiencing grade 4 toxicities, most notably grade 3/4 anemia (64 %), ifosfamide-induced encephalopathy (24 %), febrile neutropenia (40 %), and post-operative wound complications (20 %).

Response to neoadjuvant therapy

Histopathologic response

One advantage of neoadjuvant therapy is the ability to evaluate the tumor tissue response at the time of surgery. While histopathologic response to preoperative therapy has been shown to be a prognostic factor for osteosarcoma and Ewing's sarcoma, its correlation with clinical outcome is still uncertain for soft tissue sarcoma.

- A retrospective review from UCLA analyzed pathologic necrosis among 496 patients treated per sequential institutional chemoradiotherapy protocols [46]. Ten-year OS among patients with ≥95 % tumor necrosis was significantly greater than those with <95 % necrosis (71 vs 55 %, p=0.0001).
- A smaller review from the University of Chicago demonstrated improved freedom from distant metastases (85 vs. 20 %, p=0.02) in patients with ≥90 % treatment-induced necrosis [47].
- Several other series have also reported a correlation between histopathologic response and clinical outcome [48, 49].

Other series have suggested less potential value of pathologic necrosis as a prognostic marker:

- Over 200 patients were included in the University of Southern California's review of neoadjuvant therapy (chemotherapy, radiation, or both), which found that tumor necrosis ≥90 % correlated with a greater 8-year DFS (67 vs. 51 %), but did not show statistical significance on multivariate analysis (HR 0.61, p=0.051) [50].
- A recent retrospective review from MGH evaluated the outcomes of 113 patients treated per an institutional protocol and analyzed for association with percentage pathologic necrosis [51•]. Forty-four percent of patients achieved ≥95 % tumor necrosis, but 5-year DFS (85 %) and OS (85 %) were no different compared to patients with less than 95 % necrosis.

Our trial of epirubicin, ifosfamide, and hypofractionated radiotherapy was unique in using histopathologic necrosis as the primary endpoint and to our knowledge is the first prospective study to use such an endpoint in this disease state:

- Forty percent (95 % CI 21–59 %) of patients achieved ≥95 % pathologic necrosis. There was no correlation between necrosis rate and clinical outcome, but the small sample size did not permit adequate test of association [29].
- Pathologic response is a primary outcome measure of an ongoing Children's Oncology Group and NRG Oncology sponsored phase 2/3 randomized trial of preoperative chemoradiation and a tyrosine kinase inhibitor for resectable soft tissue sarcoma [52]. The increasing body of data from such studies will add clarity to the questionable prognostic value of this marker.

Imaging response

Because primary soft tissue sarcoma tumors can often be composed of viable sarcoma along with fibrosis, hemorrhage, and necrosis, significant radiographic tumor regression to preoperative treatment is uncommon and may not correlate with clinical response. There is increasing interest in developing noninvasive and quantitative imaging modalities to detect response [53, 54]. Ultimately, imaging modalities may aid in early treatment decisions, potentially indicating which non-responding patients are unlikely to benefit from further chemotherapy, or when an alternative regimen should be employed. For instance, dynamic contrast-enhanced MRI (DCE-MRI) detects changes in blood flow and blood vessel wall permeability, which may be particularly useful for assessing response to antiangiogenic agents (see "Emerging therapies" section below):

- Our group has correlated changes in DCE-MRI biomarkers early in the course of therapy with the amount of histopathologic tumor necrosis found in the eventual surgical specimen [32•]. We continue to study the utility of DCE-MRI in detecting early treatment effect from neoadjuvant therapy and collect data regarding long-term clinical outcome.

Other groups are investigating the use of [18F]fluorodeoxyglucose (FDG)-PET in STS:

- A prospective trial at UCLA evaluated FDG-PET at baseline and after one cycle of chemotherapy [55]. Using a ≥35 % reduction in FDG uptake as the response threshold, investigators were able to predict histopathologic response with a sensitivity and specificity of 100 and 67 %, respectively.
- The University of Washington conducted a similar study with the second FDG-PET obtained after two cycles of chemotherapy and were able to correlate with clinical outcome [56•]. The authors defined SUV_{diff} as the percentage change in SUV_{max} between baseline and mid-chemotherapy scans and were able to conclude that on average, for every 18 % increase in SUV_{diff}, there was an associated halving of the risk of death (i.e., the hazard ratio was approximately 0.5).
- Tateishi et al. also demonstrated that metabolic response by FDG-PET was an independent predictor of OS [49]. A SUV reduction rate between baseline and end of neoadjuvant chemotherapy of ≥60 % correlated with 2-year OS 96 % compared to 51 % (p=0.0001), which remained prognostic after multivariate analysis (HR 10.31).

Emerging therapies

Many soft tissue sarcomas demonstrate extensive abnormal angiogenesis, resulting in acute and chronic intratumoral hypoxia [36, 57–59]. Antiangiogenic therapies have a role in treating soft tissue sarcomas, with the VEGFR tyrosine kinase inhibitor pazopanib approved for use in advanced disease after demonstrating improved progression-free survival in a phase III trial [60]. One potential effect of treatment with angiogenesis inhibitors is normalization of tumor vasculature and increase in tumor tissue oxygenation

[61, 62]. Radiotherapy is most effective in well-oxygenated tissues, and therefore, the use of angiogenesis inhibition with concurrent radiation is of interest in STS and is applicable to the neoadjuvant setting.

Sorafenib

- We conducted a phase 1 trial to investigate the feasibility of sorafenib treatment as an adjunct to our chemoradiotherapy regimen with epirubicin/ifosfamide [32•]. Sorafenib 400 mg daily was established as the maximum tolerated dose and was administered continuously pre- and post-operatively. Toxicity included grade 3/4 neutropenia (94 %), hypophosphatemia (75 %), anemia (69 %), thrombocytopenia (50 %), and febrile neutropenia (50 %). Of 16 evaluable patients, there were no deaths and no local recurrences at 2 years of follow-up. Changes in DCE-MRI biomarkers were detected after 2 weeks of sorafenib treatment and correlated with eventual histopathologic response. A phase 2 trial is currently underway at Oregon Health & Science University [63].
- At UC Davis, a phase 1 trial of concurrent sorafenib and radiation without chemotherapy confirmed tolerability and reported a complete pathologic response rate of 38 % (three of eight patients) [35].
- A similar trial of sunitinib with preoperative radiation, however, resulted in unacceptable toxicities, higher local relapse rates, and premature study closure [36].

Pazopanib

- The Children's Oncology Group and NRG Oncology are conducting an intergroup phase 2/3 randomized trial of preoperative chemoradiation with or without pazopanib for the treatment of resectable STS of the extremities and trunk [52]. All non-rhabdomyosarcoma subtypes are eligible but are divided into *chemotherapy-sensitive* and *chemotherapy-resistant*. Chemotherapy-sensitive subtypes will receive doxorubicin/ifosfamide pre- and post-operatively, with neoadjuvant radiation to 4500 cGy over 25 fractions. Chemotherapy-resistant subtypes will receive neoadjuvant radiation to 5000 cGy over 25 fractions. After a dose-finding phase, each of these cohorts will be randomized to determine whether or not pazopanib will be added to the treatment regimen.

Conclusion

A regimen of preoperative chemoradiation immediately addresses issues of both local control and micrometastases and should be considered for all patients with high-risk STS of the extremities. At time of diagnosis, neoadjuvant therapy should be discussed in the context of a multidisciplinary tumor board discussion at an experienced sarcoma center.

Definitive evidence for survival benefit of neoadjuvant chemoradiation in high-risk extremity soft tissue sarcomas has been elusive. Given the relative rarity of these cancers, it is imperative that patients be enrolled on clinical trials. The addition of unique endpoints (i.e., rate of histopathologic response) and correlative studies (i.e., novel imaging or monitoring of cell-free DNA) to these trials will provide additional value.

Ultimately, we believe the survival benefit of early chemotherapy will be proven, but that the subsets of patients most likely to benefit have yet to be defined.

Compliance with Ethics Guidelines

Conflict of Interest

Lara E. Davis declares that she has no conflict of interest.

Christopher W. Ryan has received compensation from Pfizer, Onyx Pharmaceuticals, Janssen, EMD-Serono, Genentech, and Aveo for service as a consultant.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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