Systemic Therapy for Advanced Soft Tissue Sarcoma

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BACKGROUND

Sarcomas are rare tumors that arise from or are differentiated from tissues of mesodermal origin. They comprise less than 1% of all adult malignancies.1 In 2015 there were approximately 14,900 new cases diagnosed, with 6360 deaths in the United States. Sarcomas are grouped into 2 general categories: soft tissues sarcomas and primary bone sarcomas, which have different staging and treatment approaches.

This article includes a discussion of chemotherapy in advanced or refractory soft tissue sarcoma. Patients with metastatic disease are usually best managed with chemotherapy. Distant metastasis occurs in up to 10% of patients, with the lung being the most common site in 83% of cases.2 Systemic therapy can involve cytotoxic

KEYWORDS

- Advanced soft tissue sarcoma • Chemotherapy • Novel therapies

KEY POINTS

- Survival for advanced soft tissue sarcomas has improved significantly over the last 20 years because of advancements in histologic classification, improved treatment approaches, and novel agents.
- An important factor guiding choice of therapy is soft tissue sarcoma subtype, as drugs such as eribulin and trabectedin may have particular activity in leiomyosarcoma and liposarcoma.
- Focus on angiogenesis inhibition has led to the approval of pazopanib for soft tissue sarcoma, and the pathway continues to be investigated in this disease.
- Toxicity is an important area of investigation in soft tissue sarcoma, and new agents, such as aldoxorubicin, may be alternatives with better safety profiles.
- Future studies on treatment of advanced soft tissue sarcoma will continue to focus on identification of novel drug targets, personalization of therapy, and combination immunotherapies.

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chemotherapy or targeted therapy with different toxicity profiles. In general, the response rates to doxorubicin and ifosfamide have ranged from 20% to 35%, while the response to other single-agent chemotherapy is low (10% or less).\textsuperscript{3} In addition, combination and dose-intense regimens have largely failed to improve survival.\textsuperscript{4} New therapies such as eribulin, olaratumab, and immunotherapy are promising and are under further investigation.

**DOXORUBICIN**

Doxorubicin is an anthracycline antibiotic isolated from *Streptomyces peucetius*, which intercalates in the DNA helix and prevents replication.\textsuperscript{5} It has been used since the 1970s, with initial studies demonstrating a complete remission in 6.7% and partial remission in 20% of patients with metastatic soft tissue sarcoma.\textsuperscript{6} More recent studies of doxorubicin 75 mg/m\textsuperscript{2} administered every 3 weeks have demonstrated objective response rates (ORRs) ranging from 18.8% to 25.6%.\textsuperscript{7,8}

A 2001 EORTC (European Organization for Research and Treatment of Cancer) phase II trial compared Doxil (pegylated liposomal doxorubicin) 50 mg/m\textsuperscript{2} every 4 weeks with doxorubicin 75 mg/m\textsuperscript{2} every 3 weeks (Table 1). Response rates in the cohort of patients with soft tissue sarcoma excluding gastrointestinal stromal tumor were 14% and 12% for Doxil and doxorubicin, respectively. Incidents of hematologic toxicity, febrile neutropenia, and alopecia were higher in the doxorubicin arm. However, more patients had palmar–plantar erythrodysesthesia in the Doxil arm.\textsuperscript{9} Doxil has activity specifically in cutaneous angiosarcoma. A review of 8 cases in Germany demonstrated a complete response in 2 patients, partial response in 4 patients, and a response followed by progressive disease in 1 patient.\textsuperscript{10} Another retrospective analysis of 119 patients with metastatic angiosarcoma showed that doxorubicin, Doxil, and taxanes resulted in similar response rates (30%) and median overall survival (OS) of 12.1 months.\textsuperscript{11}

Response rates as high as 66% in patients receiving doxorubicin 75 to 90 mg/m\textsuperscript{2} in combination with ifosfamide have been noted.\textsuperscript{12} Combinations of Doxil and ifosfamide as first-line therapy for metastatic soft tissue sarcoma have demonstrated ORRs as high as 55.9%.\textsuperscript{13} However, a meta-analysis of 2281 patients showed that although the response rate was marginally higher for patients receiving doxorubicin and ifosfamide versus single-agent doxorubicin, pooled analysis using random effects showed no statistically significant difference. Additionally, a significant difference was not achieved with 1-year or 2-year mortality rate.\textsuperscript{14} Some of these findings are supported by the multicenter phase III trial, EORTC 62012. Patients with locally advanced, unresectable, or metastatic high-grade soft tissue sarcomas were randomly assigned to receive doxorubicin (n = 228) or doxorubicin and ifosfamide (n = 227). Doxorubicin was given at 75 mg/m\textsuperscript{2} on day 1 bolus or 72-hour infusion at 25 mg/m\textsuperscript{2}/d. In the combination arm, ifosfamide was given at 10 g/m\textsuperscript{2} over 4 days with mesna and pegfilgastrim. There was no significant difference in OS between the 2 groups (hazard ratio [HR] 0.83, 95.5% confidence interval [CI], 0.67–1.03; \(P = .076\), as OS was 12.8 months in doxorubicin group (95.5% CI, 10.5–14.3) and 14.3 months in the combination group (95.5% CI, 12.5–16.5). However, the median progression-free survival (PFS) was significantly higher for combination chemotherapy at 7.4 months (95% CI, 6.6–8.3) versus doxorubicin at 4.6 months (95% CI, 2.9–5.6); (HR 0.74, 95.5% CI, 0.60–0.90; \(P = .003\)).\textsuperscript{15}

**IFOSFAMIDE**

Ifosfamide, a nitrogen mustard alkylating agent that crosslinks DNA, has demonstrated activity in soft tissue sarcoma at doses of 7.5 g/m\textsuperscript{2} to 10 g/m\textsuperscript{2}. A phase III trial
<table>
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<tr>
<th>Author, Year</th>
<th>N</th>
<th>Subtype</th>
<th>Regimen</th>
<th>Previous Chemotherapy</th>
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<td>Judson et al, 9 2001</td>
<td>95</td>
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<td>N</td>
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<td>Doxorubicin: 12%</td>
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<td>Doxorubicin: 14% Combination: 26% (P = .0006)</td>
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<td>119</td>
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<td>Gemcitabine: 11.5 Combination: 17.9 Pr(βGD&gt; 0</td>
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<td>Y</td>
<td>Uterine LMS: Gemcitabine: 19% Combination: 24% Non-uterine LMS: Gemcitabine: 14% Combination: 5%</td>
<td>Uterine LMS: Gemcitabine: 20 Combination: 23 Non-uterine LMS: Gemcitabine: 15 Combination: 13</td>
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<td>Author, Year</td>
<td>N</td>
<td>Subtype</td>
<td>Regimen</td>
<td>Previous Chemotherapy</td>
<td>Response Rate&lt;sup&gt;a&lt;/sup&gt;</td>
<td>OS, median (months)&lt;sup&gt;b&lt;/sup&gt;</td>
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<td>Seddon, 2015</td>
<td>257</td>
<td>Advanced soft tissue sarcoma</td>
<td>Doxorubicin 75 mg/m&lt;sup&gt;2&lt;/sup&gt; every 3 wk vs gemcitabine 675 mg/m&lt;sup&gt;2&lt;/sup&gt; days 1 and 8 and docetaxel 75 mg/m&lt;sup&gt;2&lt;/sup&gt; day 8 every 3 wk</td>
<td>N</td>
<td>Includes Stable Disease: Doxorubicin: 65.9% Combination: 58.6%</td>
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<td>Buesa et al, 1991</td>
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<td>van der Graaf et al, 2012</td>
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<td>Yovine et al, 2004</td>
<td>54</td>
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<td>Y</td>
<td>3.7%</td>
<td>12.8 mo</td>
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<td>Garcia-Carbonera et al, 2004</td>
<td>36</td>
<td>Soft tissue sarcoma</td>
<td>Trabectedin 1.5 mg/m&lt;sup&gt;2&lt;/sup&gt; over 24 h every 3 wk</td>
<td>Y</td>
<td>8%</td>
<td>12.1 mo</td>
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<td>Le Cesne et al, 2005</td>
<td>104</td>
<td>Soft tissue sarcoma</td>
<td>Trabectedin 1.5 mg/m&lt;sup&gt;2&lt;/sup&gt; over 24 h every 3 wk</td>
<td>Y</td>
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<td>9.2 mo</td>
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<td>Demetri et al, 2009</td>
<td>270</td>
<td>Liposarcoma, LMS</td>
<td>Trabectedin 1.5 mg/m&lt;sup&gt;2&lt;/sup&gt; over 24-h every 3 wk vs 0.58 mg/m&lt;sup&gt;2&lt;/sup&gt; 3-h infusion every week for 3 wk of a 4-wk cycle</td>
<td>Y</td>
<td>q3 wk 24-h: 5.6% qweek 3-h: 1.6%</td>
<td>q3 wk 24-h: 13.9 qweek 3-h: 11.8</td>
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<tr>
<td>Study</td>
<td>Year</td>
<td>Patients</td>
<td>Disease</td>
<td>Treatment</td>
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<td>Median PFS (mo)</td>
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<td>Monk et al.</td>
<td>2012</td>
<td>20</td>
<td>Uterine LMS</td>
<td>Trabectedin 1.5 mg/m² over 24 h every 3 wk</td>
<td>N</td>
<td>10%</td>
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<td>Demetri et al.</td>
<td>2015</td>
<td>518</td>
<td>Liposarcoma and LMS</td>
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<td>Y</td>
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<td>Schoffski et al.</td>
<td>2011</td>
<td>128</td>
<td>LMS, synovial sarcoma, adipocytic sarcoma and other</td>
<td>Eribulin 1.4 mg/m² on days 1 and 8 of a 21 d cycle</td>
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<td>Adipocytic: 3%</td>
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<tr>
<td>Schoffski et al.</td>
<td>2015</td>
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<td>LMS, adipocytic sarcoma</td>
<td>Eribulin 1.4 mg/m² on days 1 and 8 of a 21 d cycle vs dacarbazine (850 or 1000 or 1200 mg/m²) every 3 wk</td>
<td>Y</td>
<td>Eribulin: 4%</td>
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<td>Chawla et al.</td>
<td>2015</td>
<td>13</td>
<td>Soft tissue sarcoma</td>
<td>Aldoxorubicin 350 mg/m² every 3 wk (phase II portion of trial)</td>
<td>Y</td>
<td>38%</td>
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<tr>
<td>Chawla et al.</td>
<td>2015</td>
<td>126</td>
<td>Advanced, unresectable or metastatic soft tissue sarcoma</td>
<td>Aldoxorubicin 350 mg/m² vs doxorubicin 75 mg/m² every 3 wk</td>
<td>N</td>
<td>Aldoxorubicin: 25%</td>
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<td>Tap, et al.</td>
<td>2015</td>
<td>133</td>
<td>Unresectable or metastatic soft tissue sarcoma</td>
<td>Doxorubicin (75 g/m²) with or without olaratumab (15 mg/kg on days 1 and 8) every 21 d</td>
<td>Both treated and untreated</td>
<td>Doxorubicin: 12.3%</td>
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<tr>
<td>Dickson, et al.</td>
<td>2016</td>
<td>60</td>
<td>Liposarcoma</td>
<td>Palbociclib 125 mg orally daily for 21 d in 28 d cycles</td>
<td>Both treated and untreated</td>
<td>1.6%</td>
</tr>
</tbody>
</table>

*Results are statistically nonsignificant unless otherwise specified.
*b Where specified.

_Data from Refs._ 8,9,15,16,24,25,28,29,36,38,39,42–45,47,50,53–56,58
of doxorubicin at 75 mg/m² versus ifosfamide at 9 g/m² showed no differences in PFS, OS, or response rates in a population of mostly leiomyosarcoma (LMS) and synovial sarcoma. However, grade 4 hematologic toxicity and encephalopathy were higher in the ifosfamide arm. Despite increased toxicity, exposure to higher-dose ifosfamide (>10 g/m²) per cycle has demonstrated higher rates of complete and partial responses, with overall response rates as high as 19% to 37.7%. A retrospective analysis of 1319 patients by EORTC-STBSG (Soft Tissue and Bone Sarcoma Group) identified predictive factors of response to first-line ifosfamide-containing chemotherapy. Trending found that patients with liposarcoma and LMS benefited less from ifosfamide-containing therapy compared with doxorubicin alone. The response rate for synovial sarcoma patients was higher in the ifosfamide-containing regimen, but not statistically significant. Other studies have demonstrated the sensitivity of synovial sarcoma to ifosfamide with a complete response rate of 30.7% in 13 patients. The addition of ifosfamide to doxorubicin and dacarbazine in 340 patients improved response rates (32% vs 17%; P < .002) and time to progression (TTP 6 months vs 4 months; P < .02), with no significant advantage for OS.

GEMCITABINE

Gemcitabine is a pyrimidine antimetabolite that inhibits DNA synthesis by inhibiting DNA polymerase and ribonucleotide reductase. In the United States, a phase II study of 56 patients with soft tissue sarcoma treated with gemcitabine at 2 different dose rates showed an ORR of 18% (95% CI, 7%–29%) and median duration of response of 3.5 months (range: 2–13 months). A pharmacology analysis demonstrated higher levels of gemcitabine triphosphate in peripheral blood mononuclear cells in patients receiving a fixed-dose rate infusion over 150 minutes compared with standard dosing over 30 minutes.

Gemcitabine may also be synergistic with docetaxel. A phase II trial (n = 119) conducted by Sarcoma Alliance for Research through Collaboration (SARC) compared fixed dose rate gemcitabine at 1200 mg/m² on days 1 and 8 every 21 days and fixed dose rate gemcitabine at 900 mg/m² over 90 minutes on days 1 and 8 in combination with docetaxel at 100 mg/m² over 1 hour on day 8 every 21 days. In the combination arm (n = 73), the ORR was 16% versus 8% in the single-agent arm (n = 49). The median PFS was 6.2 versus 3.0 months, and median OS was 17.9 versus 11.5 months in the combination versus single-agent arm, respectively. The posterior probability that combination therapy was superior to single-agent gemcitabine was 0.8 for PFS and 0.97 for OS. More than 40% of patients in the combination arm discontinued therapy within 6 months because of nonhematologic toxicity such as myalgia and fatigue, suggesting that cumulative toxicity with this regimen is prohibitive of long-term use. Grade 3 fatigue and myalgias or muscle weakness were observed in 25% of patients receiving combination therapy versus 10% of patients receiving gemcitabine only. Despite increase in toxicity of the combination as compared to gemcitabine alone, the authors concluded that the toxicity associated with gemcitabine and docetaxel compared favorably to the combination of doxorubicin and ifosfamide. However, a separate phase II study of LMS in France, TAXOGEM, showed no difference in ORR in uterine LMS (n = 46) and nonuterine LMS (n = 44) groups receiving gemcitabine or the combination of gemcitabine and docetaxel. A total of 90 patients received either gemcitabine at 1,000 mg/m² on days 1, 8, and 15 of a 28-day cycle (n = 44) or combination gemcitabine at 900 mg/m² on days 1 and 8 plus docetaxel at 100 mg/m² on day 8 of a 21 day cycle (n = 46). ORR in uterine LMS was 19% in the gemcitabine arm (95% CI, 5%–42%) and 24% in the combination arm (95% CI, 8%–47%). For
patients with nonuterine LMS, response rates were 14% (95% CI, 3%–35%) versus 5% (95% CI, 0%–26%). For uterine LMS, the median PFS was 5.5 months for gemcitabine and 4.7 months for the combination arm. For nonuterine LMS, the median PFS was 6.3 months for gemcitabine and 3.8 months for the combination arm. The differences in these results as compared to the SARC trial may be due to inclusion of only patients with LMS who had failed first-line anthracycline regimen, whereas the SARC trial enrolled patients with all histologies who received none or a variety of regimens. Additionally, they had different designs (Bayesian vs classical randomization), schedules for drug intensity, and staging intervals.

Other studies have also demonstrated the activity of gemcitabine and docetaxel in LMS. In a phase II study of 34 patients with LMS who had not responded to up to 2 prior regimens, the ORR was 53%, with a median TTP of 5.6 months; 52.6% of patients had received no prior therapy. Single-agent gemcitabine has also shown activity in angiosarcoma. In a retrospective case series of 25 patients with advanced angiosarcoma, there was an ORR of 68%, median OS of 17 months, and median PFS of 7 months (range: 1–40 months), suggesting that some patients may attain long-lasting responses.

A phase III trial of gemcitabine and docetaxel with doxorubicin for soft tissue sarcomas (GeDDiS), compared gemcitabine and docetaxel with doxorubicin as first-line treatment in previously untreated advanced soft tissue sarcoma. Patients were randomized to receive 6 cycles of doxorubicin at 75 mg/m² day 1 every 3 weeks (n = 129) or gemcitabine 675 mg/m² intravenously on days 1 and 8 and docetaxel 75 mg/m² intravenously on day 8 every 3 weeks (n = 128). The primary endpoint of PFS at 24 weeks was achieved in 46.1% of the doxorubicin arm and 46.0% of the combination arm (HR 1.28, 95% CI, 0.98–1.67; P = .07). Median OS was 71 versus 63 weeks (HR 1.07; 95% CI, 0.77–1.49) for doxorubicin versus combination. Although PFS Kaplan-Meier curves did not violate the proportional hazards assumption (P = .53), they initially overlapped and then separated after 24 weeks in favor of doxorubicin. Patients receiving doxorubicin had higher grade 3 and 4 toxicities of febrile neutropenia and mucositis, while patients receiving combination had higher grade 3 and 4 rates of fatigue and diarrhea. The combination arm was also associated with greater dose delays of at least 1 day, patient withdrawal due to toxicity and lower mean dose intensity despite a lower starting dose of gemcitabine and docetaxel than previously published. Therefore, the investigators suggested that doxorubicin should be the preferred agent for first-line treatment in advanced soft tissue sarcoma.

**DACARBAZINE AND TEMOZOLOMIDE**

Dacarbazine is an alkylating agent that breaks DNA strands. In a phase II EORTC study of 44 patients with advanced soft tissue sarcoma who had received previous chemotherapy, 1 complete remission and 7 partial remissions were seen with dacarbazine, for a response rate of 18%. Median duration of response was 8 weeks, with complete remission lasting 12 months. Other investigators have suggested that second- or third-line dacarbazine may have comparable activity to other treatments but with a better profile toxicity. The combination of doxorubicin and dacarbazine has yielded a response rate of 17%.

Temozolomide is an oral agent and prodrug of the active metabolite of dacarbazine. An initial phase II study of temozolomide in soft tissue sarcoma (n = 41) suggested that it was well tolerated at a dose of 85 mg/m² orally for 21 days on a 28-day cycle. However, it had minimal efficacy (response rate of 5%) and a limited role in soft tissue sarcoma. In a phase II study by the Spanish Group for Research on
Sarcomas, 49 patients with pretreated soft tissue sarcoma were given temozolomide 75 to 100 mg/m² continuously (doses were dependent on time of enrollment into the study due to an amendment). The response rate was 15.5%, most notable in patients with gynecologic LMS. 33 The activity of temozolomide may be higher in patients with tumors lacking MGMT (O6-methylguanine-DNA methyltransferase) gene expression. Retrospective analysis of 28 patients with metastatic LMS receiving temozolomide at 75 mg/m² daily for 21 days in 28-day cycles yielded an overall response rate of 17.8%. Median PFS was 126 days. MGMT was deficient in tumors from 6 of 20 patients with clinical benefit and in 1 of 8 without clinical benefit. Median PFS was 105 days for the MGMT-intact group and 203 days for the MGMT-deficient group. 34

**PACLITAXEL**

Paclitaxel promotes microtubule assembly and interferes with cell replication by stabilizing existing microtubules. Paclitaxel is useful in treating several solid tumors and has demonstrated activity in angiosarcoma, especially of the scalp or face.

A phase II study of 28 patients with advanced soft tissue sarcoma treated with paclitaxel yielded only 2 partial responses. The responding patients included 1 patient with angiosarcoma and uterine LMS. Therefore, the activity of paclitaxel outside of angiosarcoma appears to be low. Two patients with angiosarcoma of the scalp who did not qualify for this study were treated with paclitaxel off protocol and experienced dramatic tumor regression. In another retrospective cohort of cutaneous angiosarcoma of the head and neck treated with single-agent paclitaxel at 250 mg/m² over 3 hours every 3 weeks, there was an ORR of 88.9% in 9 patients, with a clinical complete response in 4 patients. Median duration of response was 5 months (range: 2–13 months). 35 The phase II ANGIOTAX study of 30 patients with unresectable angiosarcoma formally evaluated the activity of paclitaxel in angiosarcoma. The agent was given at 80 mg/m², 3 weeks of 4. PFS at 2 and 4 months was 74% and 45%, respectively. With a median follow-up of 8 months, the median TTP was 4 months, and the median OS was 8 months. 36

A retrospective study compared doxorubicin and paclitaxel in 117 patients with angiosarcoma treated in the first-line setting. The rates of complete response, partial response, and stable disease were 6%, 23.5%, and 29.5% in the doxorubicin group and 13%, 40%, and 29.5% in the paclitaxel group. Patients in the paclitaxel group were more likely to have a cutaneous angiosarcoma. Therefore, both agents appear to have similar activity in previously untreated angiosarcoma. 37

**PAZOPANIB**

Pazopanib, a multitargeted tyrosine kinase inhibitor that limits tumor growth through inhibition of angiogenesis, has single-agent activity in advanced nonadipocytic STS. It is given as 800 mg orally once daily. In EORTC 62043, a phase II study, 142 patients with intermediate- or high-grade advanced STS who were ineligible for chemotherapy or who had received no more than 2 prior cytotoxic agents were given pazopanib. The primary endpoint was progression-free rate (PFR) at 12 weeks. The study met the predetermined cutoff for sufficient activity in 3 cohorts, with a PFR at 12 weeks of 44% for LMS (18 of 41 patients), 49% for synovial sarcoma (18 of 37 patients) and 39% in other STS types (16 of 41 patients). The study was closed in the adipocytic cohort of 19 patients after the first stage, given insufficient activity (primary endpoint achieved in only 26% of patients). 38 Another study, PALETTE (Pazopanib for metastatic soft-tissue sarcoma), an international, multicenter phase III study, randomized patients with
angiogenesis inhibitor-naïve, pretreated metastatic STS, to receive pazopanib (n = 246) or placebo (n = 123). Median PFS was significant at 4.6 months with pazopanib (95.5% CI, 3.7–4.8) versus 1.6 months with placebo (95.5% CI, 0.9–1.8; HR 0.31, 95.5% CI, 0.24–0.40; P < .0001). OS was not statistically different at 12.5 months with pazopanib (95.5% CI, 10.6–14.8) versus 10.7 months with placebo (95.5% CI, 8.7–12.8).39

In a pooled analysis of both the EORTC 62043 (n = 118) and PALETTE (n = 226), PFS was 4.4 months, and median OS was 11.7 months. One hundred twenty-four patients (36%) had a PFS greater than 6 months. One hundred sixteen patients (34%) survived more than 18 months. A total of 12 patients remained on pazopanib for over 2 years.40 Additional studies are investigating the activity of pazopanib in liposarcoma and in combination with other therapies.

TRABECTEDIN

Trabectedin is a marine-derived compound that blocks the cell cycle by binding to the minor DNA groove, given at 1.5 mg/m^2 over 24 hours once every 3 weeks.41 In a phase II European study, 54 patients with previously treated metastatic soft tissue sarcoma demonstrated an ORR of 3.7% by World Health Organization (WHO) criteria, with a median PFS of 1.9 months and median OS of 12.8 months. The PFR at 6 months was 24%.42 In a phase II study in the United States, 36 patients with previously treated STS had an ORR of 8%, with TTP of 1.7 months and OS of 12.1 months. Notably, some responses were durable for up to 20 months.43 The EORTC phase II study of trabectedin showed that the 6-month PFS (29%) compared favorably with other drugs tested as second-line chemotherapy. Of 104 patients with pretreated advanced STS, the progression arrest rate (sum of partial response and no change in disease) was 56% in LMS and 61% in synovial sarcoma. Toxicity involved reversible grade 3 to 4 asymptomatic elevation of transaminases (40%) and neutropenia (52%).44 Another study evaluated different treatment regimens. It was a multicenter phase II study that randomized patients with pretreated liposarcomas and LMS to either trabectedin 1.5 mg/m^2 24-hour infusion once every 3 weeks (n = 136) or 0.58 mg/m^2 3-hour infusion every week for 3 weeks of a 4-week period (n = 134). The primary endpoint of median TTP was 3.7 months versus 2.3 months (HR 0.734; 95% CI, 0.554–0.974; P = .0302), favoring the every 3 weeks 24-hour arm. Median PFS was 3.3 months in the 24-hour arm versus 2.3 months in 3-hour arm (HR 0.755; 95% CI, 0.574–0.992; P = .0418).45

Trabectedin has also shown activity in the first-line setting. In 36 patients with previously untreated disease, the ORR was 17.1%, with an estimated 1-year PFS of 21% (95% CI, 11%–41%) and OS rate of 72% (95% CI, 59%–88%).41 In the worldwide expanded access program of trabectedin, efficacy data on 807 patients with refractory disease were available. A stable disease rate of 43% was reported. Patients with LMS and liposarcoma demonstrated longer OS compared with other histologies, with OS of 16.2 months (95% CI, 14.1–19.5 months). They also had a higher ORR of 6.9% (95% CI, 4.8–9.6) versus 4.0% (95% CI, 2.1–6.8) for other histologies.46 In a multicenter phase IIb study comparing single-agent doxorubicin (n = 43) with trabectedin (n = 47 for 3-hour infusion arm and n = 43 for 24-hour infusion arm), no significant improvement in PFS was observed in the trabectedin arm compared with the doxorubicin arm; therefore the study was terminated early.47

Liposarcomas and LMS are particularly sensitive to trabectedin. A phase II evaluation in 20 chemotherapy-naïve patients with advanced, persistent, or recurrent uterine LMS had a partial response noted in 10% of patients. Although there was a modest
response rate, it is noteworthy that 50% of patients achieved stable disease with a PFS of 5.8 months. More than half the patients remained in the study for more than 10 cycles (>6 months). Retrospective analysis of 5 phase II studies including 62 patients with pretreated advanced uterine LMS demonstrated a median PFS of 2.5 months (95% CI, 1.7–4.2). The primary endpoint of PFS at 6 months was achieved in 30.7% (95% CI, 19–43). Median OS was 12.1 months, with 52% alive at 12 months (95% CI, 39–64) and 20% alive at 24 months (95% CI, 10–30). A retrospective analysis of 32 patients with myxoid liposarcoma receiving trabectedin demonstrated an ORR by RECIST of 50%, with a median PFS of 17 months (95% CI, 13.5–30.1) and a median OS that was not reached.

In the multicenter phase III trial of previously treated patients with liposarcoma and LMS, trabectedin (n = 345) reduced risk of disease progression or death by 45% compared with dacarbazine (n = 173). Patients receiving trabectedin had a median PFS of 4.2 months versus 1.5 months with dacarbazine (HR 0.55, P < .001). The ORR was 9.9% versus 6.9%, respectively, with trabectedin and dacarbazine (P = .33). The clinical benefit rates (partial response, complete response, or stable disease ≥18 weeks) were 34% and 19%, respectively (P < .001). Median OS was not significant, as it was similar across both arms at 12.4 months with trabectedin and 12.9 months with dacarbazine (HR 0.87, P = .37). This study led to US Food and Drug Administration (FDA) approval of trabectedin in the United States for patients with LMS or liposarcoma previously treated with doxorubicin. Both the phase II and III studies demonstrated that the most common grade 3 to 4 adverse effects with trabectedin are related to myelosuppression and transient transaminitis.

NEOADJUVANT CHEMOTHERAPY FOR LOCALLY ADVANCED SOFT TISSUE SARCOMA

When managing patients with unresectable or borderline resectable localized soft tissue sarcoma, chemotherapy is often considered with the hope that sufficient cytoreduction will be achieved in order to convert the disease to resectable and/or to eradicate micrometastases. In a randomized study assessing the utility of neoadjuvant chemotherapy, patients with potentially radically resectable tumors were randomized to 3 cycles of preoperative chemotherapy with doxorubicin (50 mg/m²) and ifosfamide (5 g/m²) every 21 days or to no chemotherapy. Patients were required to have tumors that were at least 8 cm of any grade, or grade II/III tumors that were locally recurrent or required a second resection. Although there were no survival benefits, 29% of patients had a response (8% with a complete response), and none of the 18% of patients with progressive disease lost their surgical window or had a change in the scope of the procedure required. Another randomized phase II study focused on differences in safety outcomes for 2 different chemotherapy regimens, doxorubicin and ifosfamide versus gemcitabine and docetaxel, given neoadjuvantly for resectable soft tissue sarcoma. The response rate with doxorubicin-based chemotherapy was 12.5%, and with gemcitabine-based chemotherapy, it was 3.4%. Trabectedin has also been studied when given in the neoadjuvant fashion in 23 patients with myxoid liposarcoma, a histology known to be sensitive to this chemotherapy. Patients were required to have stage III disease for enrollment, and 17% had tumors greater than 10 cm. There was an ORR of 24%, with 13% of patients achieving a pathologic complete response. Importantly, no patients had progressive disease. None of these studies specifically address whether patients whose tumors were unresectable could be rendered surgically resectable or if the scope of surgery could be down-staged with preoperative chemotherapy.
INVESTIGATIONAL AGENTS

**Eribulin**

Eribulin, a cytotoxic agent approved for advanced breast cancer, has demonstrated improvement in OS for patients with advanced STS. It is a nontaxane microtubule inhibitor dosed at 1.4 mg/m² on days 1 and 8 of a 21-day cycle. A phase II study included 128 patients who had received no more than 1 previous combination chemotherapy or up to 2 single agents. Patients were stratified by histology: LMS (n = 40), synovial sarcoma (n = 19), adipocytic sarcoma (n = 37), and other sarcomas (n = 32). Only the LMS and liposarcoma cohorts met the primary endpoint of PFS at 12 weeks; 31.6% of patients with LMS and 46.9% with adipocytic sarcoma were progression free at 12 weeks. In the other groups, only 21.1% with synovial sarcoma and 19.2% with other sarcomas were progression free at 12 weeks.

In a follow-up multicenter phase III trial, 452 patients with pretreated advanced LMS or adipocytic sarcoma were randomized to receive eribulin or dacarbazine. The primary endpoint was OS, which was significantly improved with eribulin. Median PFS was 2.6 months in both arms (HR 0.877, 95.5% CI, 0.710–1.085; P = .229). The median OS was 13.5 months with eribulin compared with 11.5 months with dacarbazine (HR 0.768, 95.5% CI, 0.618–0.954; P = .017). The 12-week PFS rate was 33% with eribulin and 29% with dacarbazine; however, this difference was not statistically significant. In the eribulin arm, 26% of patients required dose reductions, and 8% discontinued due to treatment-emergent adverse events (TEAEs) versus 14% and 5% in the dacarbazine arm, respectively. These TEAEs included neutropenia, pyrexia, peripheral sensory neuropathy, and alopecia.

**Aldoxorubicin**

Aldoxorubicin is an albumin-binding prodrug of doxorubicin that has promising activity in advanced soft tissue sarcoma. A phase Ib/II study of aldoxorubicin included 17 patients (68%) with advanced soft tissue sarcoma, of whom 13 received aldoxorubicin at the maximum tolerated dose (MTD) of 350 mg/m². Among these patients, a partial response was achieved in 38% and stable disease in 46%. In the subsequent international phase IIb study, 123 patients with previously untreated locally advanced, unresectable, or metastatic soft tissue sarcoma were randomized to aldoxorubicin at 350 mg/m² (n = 83) or doxorubicin 75 mg/m² (n = 40) once every 3 weeks for up to 6 cycles. Median PFS was significantly in favor of the aldoxorubicin arm: 5.6 months with aldoxorubicin (95.5% CI, 3.0–8.1) versus 2.7 months with doxorubicin (95.5% CI, 1.6–4.3) (P = .02). The rate of 6-month PFS was 46% versus 23% (P = .02). Median OS was not statistically different between the groups. Overall tumor response rate was higher with aldoxorubicin than with doxorubicin (25% vs 0%), as 20 patients achieved partial response with aldoxorubicin. No patient in either arm developed congestive heart failure or clinically significant abnormal cardiac function as measured by echocardiography or multigated acquisition scan. Three of 40 patients who received doxorubicin had a left ventricular ejection fraction (LVEF) that dropped below 50% while participating in the study. Twelve percent of patients in the aldoxorubicin group and 29% of patients in the doxorubicin group had at least a 10% decrease in LVEF at some point during treatment. A phase III confirmatory trial comparing aldoxorubicin with physician choice chemotherapy recently completed enrollment, and results are awaited.

**Olaratumab**

Olaratumab (IMC-3G3) is a human antiplatelet-derived growth factor alpha (PDGFRα) monoclonal antibody that blocks ligand binding. A randomized phase Ib/II study
evaluated the efficacy of doxorubicin (75 g/m² on day 1) with or without olaratumab (15 mg/kg on days 1 and 8 every 21 days) for up to 8 cycles in advanced STS. Patients randomized to the olaratumab arm were allowed to receive maintenance olaratumab until disease progression. Of 133 patients, median PFS was 6.6 months in the combination arm and 4.1 months in doxorubicin alone (HR 0.672; 95.5% CI, 0.442–1.021; \( P = .0615 \)). Interim median OS was 25.0 months with combination therapy and 14.7 months with doxorubicin alone (HR 0.44, \( P = .0005 \)). The study met its primary PFS endpoint and achieved an impressive 10.3 month improvement in median OS. Grade 3 or 4 adverse events occurred in over 5% of the population. Those in the olaratumab arm experienced neutropenia (51.5%), anemia (12.5%), fatigue (9.4%), and thrombocytopenia (9.4%), but had lower rates of febrile neutropenia (12.5%) and infections (6.3%). Overall, 64% of patients in the combination arm had a grade 3 or 4 adverse event, compared with 54% in the doxorubicin arm. Discontinuation of therapy was noted in 8 patients in the combination arm (including 4 with serious adverse events) versus 14 patients in the doxorubicin arm (including 8 with serious adverse events). A phase III trial with a similar design is currently enrolling patients.

**Palbociclib**

In the mammalian cell cycle, G1 to S phase transition is tightly regulated by cyclin-dependent kinases 4 and 6 (CDK4/6). Palbociclib is a selective CDK4/CDK6 inhibitor. CDK4 is amplified in the majority of well-differentiated and dedifferentiated liposarcomas. In an open-label study of palbociclib 200 mg orally daily for 14 of 21 days, the PFS at 12 weeks was 66% (90% CI, 51–100) with a median PFS of 18 weeks. However, there was a high rate of hematologic toxicity, with 24% of patients requiring a dose reduction. A subsequent study evaluated an alternate dosing regimen of palbociclib at 125 mg daily for 21 days in 28-day cycles. This dosing schedule was associated with less hematologic toxicity, as only 5% of patients required a dose reduction for this reason. The efficacy was comparable to the 200 mg dose.

**SUMMARY**

The French Sarcoma Group has shown that on retrospective multivariate analysis, median OS for advanced STS has improved by 50% in the last 20 years. Contributing factors to this are the advancements in histologic and molecular classification of soft tissue sarcoma and improvements in treatment paradigms, as well as the development of new agents. Specific soft tissue sarcoma subtype is one of the most important factors to guide choice of therapy, as drugs such as trabectedin and eribulin have shown particular activity in LMS and liposarcoma. Inhibition of signaling pathways related to angiogenesis has been effective therapeutically in soft tissue sarcoma with pazopanib, and is now under further investigation with olaratumab. Finally, mitigating toxicity has also been an important avenue of investigation in soft tissue sarcoma, with drugs such as aldoxorubicin. Unfortunately, investigation of prodrugs and/or metabolites of ifosfamide with potentially less toxicity has largely been unsuccessful thus far. In the future, studies will continue to focus on immunotherapy approaches for the management of, soft tissue sarcoma as well as personalization of therapy through identification of biomarkers of activity.

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