New Therapeutic Strategies for Soft Tissue Sarcomas

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Opinion statement

The treatment of patients with metastatic soft tissue sarcomas (STS) is complex. There are limited agents available and many are associated with significant toxicity. When evaluating a patient with metastatic disease, physicians should ask themselves whether there is a role for surgery to render the patient free of disease. Combination chemotherapy in patients who have not received chemotherapy in the adjuvant setting is one option, particularly in a young patient with a good performance status. Sequential single-agent therapy for patients who are more elderly or debilitated by their disease may be more appropriate. Gemcitabine appears to be an agent with activity, particularly in patients with leiomyosarcomas. The data regarding prolonged gemcitabine infusions suggest improved activity that was predicted based on prolonged intracellular gemcitabine levels. Because of these data, the prolonged infusion schedule should be used. In addition, because of the paucity of effective agents, consideration of clinical trial participation for patients with newly diagnosed metastatic disease is appropriate, particularly in chemotherapy-insensitive histologies. The role of the newer agents (eg, ecteinascidin-743, epothilones, and mammalian target of rapamycin) is undefined. Ecteinascidin-743 has been the most extensively tested agent, and its ability to slow growth kinetics of a tumor and stabilize it clinically is intriguing. Data regarding the response to BMS-247550 will be published shortly and will help define the further role of epothilones in this disease. There is a preclinical rationale that makes the mammalian target of rapamycin inhibitors attractive for the treatment of muscle-derived neoplasms. In addition, there are cell-line data suggesting activity in rhabdomyosarcoma. These agents are being tested in adult STS and will likely be tested in pediatric histologies when there are more safety data available in that population. SU11248 will continue to be tested in patients refractory to imatinib mesylate and may well prove to be another active agent for patients with gastrointestinal stromal tumors. As depicted by the analysis of gemcitabine efficacy, agents with activity in a subgroup of STS may be overlooked by the "come one come all" approach to clinical trials in STS. Identifying key targets in specific STS will be helpful in the testing of newer molecularly targeted agents. Biologic differences will support histology-specific trials to better understand the activity of an agent in a specific disease site or specifically target a biologic pathway with relevance to the malignant potential of the disease. For future clinical trials in STS to achieve the goal of histology-specific trials, cooperative group and multi-institutional trials will be required to obtain the appropriate patients with these rare histologies. It will also be increasingly important to be committed to obtaining tumor tissue in these patients to validate hypotheses regarding tumor biology and the effectiveness of therapeutic agents.
**Introduction**

Soft tissue sarcomas (STS) are an uncommon and challenging set of diseases. They are histologically and biologically heterogeneous. Primary therapy of these tumors involves surgical resection often in conjunction with radiation therapy. Chemotherapy has been primarily relegated to the metastatic disease setting. Standard therapy with doxorubicin, ifosfamide, and dacarbazine alone or in combination has reported response rates up to 35% [1]. Recent trials evaluating novel combination therapies incorporating gemcitabine have demonstrated impressive results. In addition, novel targeted therapies are being tested in metastatic disease. This article reviews data on the role of gemcitabine alone and in combination with other agents, in addition to new therapeutic agents under investigation in STS (eg, ecteinascidin-743 [ET-743], PS-341, epothilones, and CCI-779). Preliminary results of the multitargeted tyrosine kinase inhibitor SU11248 in patients with imatinib mesylate refractory gastrointestinal stromal tumors (GIST) are presented. Novel immunologic approaches for STS are also discussed.

**Treatment**

The role of gemcitabine in soft tissue sarcoma

**Gemcitabine as a single agent in soft tissue sarcoma**

- Gemcitabine hydrochloride is a pyrimidine nucleoside analogue that inhibits DNA replication and synthesis. It is a prodrug that requires intracellular phosphorylation to derive di- and triphosphate compounds. These inhibit ribonucleotide reductase and terminate DNA synthesis when the triphosphorylated compound is incorporated into DNA [2,3]. Phase II clinical trials have evaluated the efficacy of gemcitabine in STS in first- and second-line metastatic disease (Table 1). The low overall response rate for these trials, which treated a spectrum of STS, ranges from 3.3% to 18% [4•,5]. If clinicians evaluate the response in distinct histologies, there are interesting trends to be noted (Table 2). As expected, leiomyosarcoma and liposarcomas were well represented in the patient populations of these studies. There appears to be activity in leiomyosarcomas, although not in gastrointestinal leiomyosarcomas, and there was no activity in liposarcomas. In a small population of angiosarcomas, malignant fibrous histiocytomas (MFHs), and spindle cell sarcomas, response rates greater than 10% were noted, although the number of patients treated with each histology was limited. It should be underscored that the trials with the highest reported response rates for gemcitabine were heavily weighted toward leiomyosarcoma in contrast to trials with the lowest response rates, and most of the responses noted were in uterine leiomyosarcoma [5•,6].

**Combination therapy with gemcitabine in soft tissue sarcoma**

- The activity of gemcitabine in leiomyosarcoma has been further supported by the phase II trial reported by Hensley et al. [7•], which combined gemcitabine with docetaxel in patients with uterine or nonuterine leiomyosarcoma. Thirty-four patients were enrolled (85% of patients had uterine primaries). The combination was selected because of the novel mechanisms of action of these agents compared to standard sarcoma therapeutics. Patients received gemcitabine 900 mg/m² on days 1 and 8 and docetaxel 100 mg/m² on day 8. Patients with prior pelvic radiation were treated with a 25% dose reduction of both agents. All of the patients received granulocyte colony-stimulating factor on days 9 to 15. In addition, to prolong the exposure of intracellular phosphorylated gemcitabine metabolites, the rate of infusion of the gemcitabine was increased from 30 minutes to 90 minutes. Thirty-four patients with metastatic disease were treated (14 patients had prior radiation therapy and 16 had progressed after doxorubicin-based chemotherapy). The response rate in this