New Therapeutics for Soft-Tissue Sarcomas in Adults

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By Margaret Von Mehren, MD [1]

We now have multiple novel agents that warrant testing in this disease setting. Clinical trials need not only test interesting drugs, but should also correlate information from tumor specimens and clinical responses.

Soft-tissue sarcomas are an uncommon set of malignancies that pose a therapeutic challenge. Representing a mixture of multiple histologies, approximately 9,000 cases were newly diagnosed in the United States in 2006. We are limited in our biologic understanding of these tumors because of a paucity of preclinical models and cell lines to evaluate in the laboratory. The standard chemotherapies that have been used in the treatment of these tumors—doxorubicin, ifosfamide, and dacarbazine—produce response rates that range from 18% to 27% when used as single agents.[1] Combination therapy, including newer regimens with gemcitabine (Gemzar) and docetaxel, have demonstrated higher response rates.[2] However, these regimens have not yet been tested in randomized trials to assess whether they lead to improved overall survival in the adjuvant or metastatic disease setting.

Therefore, we are in need of newer agents for the management of these malignancies. Ideally, such agents would have limited normal organ toxicity, target biologically relevant tumor targets for growth and survival, and, when combined with other therapies, have nonoverlapping toxicities. The following review will highlight new therapies, focusing on antiangiogenic agents, mammalian target of rapamycin (mTOR) inhibitors, and tyrosine kinase inhibitors (TKIs).

Cytotoxic Chemotherapy

Trabectedin (ET-743, Yondelis) is a novel alkylating chemotherapy agent that binds to the minor groove of DNA. It appears to produce its cytopathic effect via inhibition of specific transcription factor activation and is more effective in patients with abnormalities in nucleotide excision repair.[3] Derived from the sea squirt Ecteinascidia turbinata, this agent first showed activity in sarcomas in a phase I study employing a 24-hour continuous infusion. Several patients with sarcomas had long-term disease stabilization as well as responses. A compassionate use trial again demonstrated long-term stable disease in heavily pretreated patients receiving this agent.[4,5] Subsequent phase II studies have shown a 4% to 8% response rate in previously treated patients as well as minor responses in an additional 6% to 8%.[6-8] Intriguingly, one of these studies showed a 26% 6-month progression-free survival rate. This agent has been shown in vitro to have synergy with other chemotherapy agents,[9-11] and phase I studies have evaluated combinations with doxorubicin, gemcitabine, cisplatin, and taxanes. Available data from these studies suggest that such combinations can be given with some activity noted in soft-tissue sarcomas.[12,13]

Antiangiogenic Therapies

Targeting vasculature in sarcomas is a reasonable therapeutic approach, given that these tumors...
are vascular and spread hematogenously. In addition, prognosis in patients with some high-grade tumors has been shown to be correlated with levels of circulating vascular endothelial growth factor (VEGF) and/or VEGF receptor (VEGFR) expression.[14,15] Bevacizumab (Avastin), a humanized monoclonal antibody, has been shown to enhance progression-free and overall survival in patients with epithelial tumors when given with chemotherapy compared with chemotherapy alone in the metastatic disease setting.[16] This agent binds circulating VEGF, removing the ligand of VEGFR and thus removing the stimulus for growth of new blood vessels (see Figure 1).

D'Adamo and colleagues evaluated bevacizumab in combination with doxorubicin in patients with metastatic or unresectable soft-tissue sarcomas.[17] The combination resulted in only a 16% response rate in patients who were anthracycline-naive, 30% of whom had received one prior chemotherapeutic regimen. In addition, four patients had a grade 2 or worse decline in ejection fraction following one to four cycles of therapy, at doses of 75 to 300 mg/m² of doxorubicin, thus limiting its utility. Other ongoing trials are evaluating the combination of bevacizumab with gemcitabine/docetaxel, and with radiation therapy for intermediate- to high-grade sarcomas. Lastly, an ongoing phase II trial is evaluating bevacizumab as a single agent in patients with angiosarcomas.

The Radiation Therapy Oncology Group is evaluating the role of thalidomide (Thalomid) with radiation (RTOG 0330), in two cohorts of patients. The first is testing radiation and thalidomide alone preoperatively for low-grade extremity and trunk sarcomas. Following resection, tumors resected with a positive margin receive further radiation as a boost with thalidomide. All patients then receive an additional 6 months of thalidomide. For patients with intermediate- to high-grade tumors, radiation therapy and thalidomide are being interdigitated between three preoperative cycles of MAID chemotherapy (mesna, doxorubicin [Adriamycin], ifosfamide, dacarbazine). Following resection, postoperative radiation is given with thalidomide to those with positive margins, and thalidomide is continued for an additional 12 months. This study incorporates circulating endothelial cells as a potential biomarker of efficacy.

**mTOR Inhibitors**

mTOR is a central component of signaling pathways leading to induction of protein synthesis, cell proliferation, and cell-cycle progression (see Figure 1). Recently, temsirolimus (CCI-779) was shown to significantly improve overall survival in patients with renal cell carcinoma.[18] Okuno and colleagues evaluated this agent in metastatic soft-tissue sarcomas.[19] Chemotherapy-naive patients with advanced unresectable soft-tissue sarcomas were treated with weekly infusions of CCI-779. In 37 treated patients, there was only one partial response in a patient with fibrosarcoma. The median time to progression was estimated to be 2 months.

In contrast, AP23573, an analog of rapamycin, demonstrated benefit in four patient cohorts—those with bone sarcomas, liposarcomas, leiomyosarcomas, and mixed soft-tissue sarcomas.[20] The agent is given intravenously daily for 5 days every other week. Similarly to CCI-779, AP23573 produced a low response rate, with four partial responses in the bone sarcoma cohort and one in the cohort of mixed sarcomas. However, 23% to 33% of patients also had a clinical benefit, defined as a measurable clinical response or stable disease for more than 4 months. This compares favorably with the progression-free survival rates for active drugs in sarcomas from data published by the European Organisation for Research and Treatment of Cancer (EORTC).[21] The differences in benefit associated with these two mTOR inhibitors may be due to inherent differences in the drugs or possibly differences in mTOR inhibition caused by the different dosing regimens. Ideally, agents should not only result in disease stabilization, but tumor response. Further testing of AP23573 in combination with systemic agents may result in improved measurable responses. This agent is being fast-tracked for approval by the US Food and Drug Administration (FDA) for the treatment of advanced sarcomas.

**Tyrosine Kinase Inhibitors**

TKI therapy has been shown to benefit patients with various carcinomas in both the metastatic and adjuvant disease settings. These agents function by inhibiting growth factor receptors or their signaling partners, thereby turning off growth signals (see Figure 1). The management of metastatic gastrointestinal stromal tumor (GIST) has been significantly improved by the use of imatinib mesylate (Gleevec), which inhibits KIT, platelet-derived growth factor receptor (PDGFR), ABL, and TEL, and has served as a paradigm for the potential of targeted therapies. That said, GIST differs from most other malignancies, including other sarcomas. Biologically, GIST is driven by constitutive activation of the growth factors KIT or PDGFR, which occurs as a result of mutations in the
corresponding genes. Unfortunately, we are unaware of relevant biologic targets in the majority of other sarcomas, and those that have been identified have not demonstrated significant clinical benefit when they have been targeted.

Imatinib has been tested in various sarcomas other than GIST. The greatest activity has been seen in dermatofibrosarcoma protuberans (DFSP), a cutaneous sarcoma that infrequently metastasizes. This tumor contains a characteristic translocation of chromosomes 17 and 22, resulting in a fusion protein of collagen 1A1 with PDGFR-beta.[22] Imatinib, which inhibits PDGFR, has benefited patients with large primary tumors and metastatic disease. The drug is the focus of ongoing clinical trials in DFSP and was recently approved for this indication by the FDA. Desmoid tumors have also been shown to potentially benefit from imatinib therapy, primarily as a consequence of tumor stabilization.[23,24] The underlying mechanism for this clinical finding is not clear.

Soft-tissue and bone sarcomas have been shown to express members of the epidermal growth factor receptor (EGFR) family. EGFR has been demonstrated on malignant peripheral nerve sheath tumors (MPNST), a rare type of sarcoma that occurs more commonly in patients with neurofibromatosis type I.[25] A recent trial evaluated the benefit of erlotinib (Tarceva) in patients with metastatic or unresectable MPNST but found no clinical activity.[26] Synovial sarcomas have also been shown to express EGFR as well as HER2/neu. A phase II trial of gefitinib (Iressa) was also disappointing, with only 13% of patients having prolonged disease stabilization.[27]

Sorafenib (Nexavar) is a multitargeted tyrosine kinase inhibitor. It is a potent inhibitor of c-raf, wild type and mutated b-raf, as well as an inhibitor of VEGFR, FLT3, PDGFR, and KIT, and a member of the MAPK family (p38a). In addition, sorafenib is an inhibitor of adenosine A3, dopamine D1, and muscarinic receptors, although the relevance of these receptors to sarcoma therapy is not evident. This agent is undergoing testing for metastatic sarcomas in several US trials.

Preclinical and clinical evidence suggests that in sarcomas deriving from malignant vasculature, such as angiosarcomas and hemangiendotheliomas, as well as high-grade leiomyosarcomas and liposarcomas, VEGF and VEGFR are present and possibly biologically relevant. The hypothesis underlying the Intergroup Coalition Against Sarcomas (ICAS) study S0505 is that inhibiting VEGFR may result in clinical benefit. Biopsies are being obtained to assess the change in phosphorylation of VEGFR, PDGFR, KIT, raf, mek and erk. It is anticipated that sorafenib and other TKIs will likely lead to prolonged disease stabilization when used as single agents. Their role in the future may be to aid in palliation of metastatic disease. However, combining these agents with chemotherapy, if found to be safe, may improve disease-free and overall survival.

**Conclusions**

Sarcomas are challenging tumors to treat, particularly when they are metastatic or unresectable. Our treatment options for these patients are currently limited to palliative radiation therapy and chemotherapy, with low response rates. However, we now have multiple novel agents that warrant testing in this disease setting. Patients with unresectable disease should be enrolled in clinical trials. Because of the limited preclinical data available, it has been difficult to rationally design therapeutic trials. Therefore, clinical trials need not only test interesting drugs, but should also correlate information from tumor specimens and clinical responses to help elucidate why a therapeutic benefit (or a lack thereof) is observed.

*This article is part of a series based on the proceedings of a special symposium of the Intergroup Coalition Against Sarcomas, "Progress in Translational and Clinical Research for Sarcomas of Adults," which was held October 8, 2006, in Seattle. The series is guest edited by Margaret von Mehren, md, Director of Sarcoma Oncology at Fox Chase Cancer Center, Philadelphia.*

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