Progress in the Systemic Treatment of Advanced Soft-Tissue Sarcomas

Scott H. Okuno, MD, and John H. Edmonson, MD

Background: Despite the plethora of chemotherapeutic remedies for advanced soft-tissue sarcomas, little evidence has developed to indicate that these efforts have been curative. No controlled comparison has yet proven that patients receiving multidrug regimens survive longer than those receiving doxorubicin alone.

Methods: The authors review current systemic treatments and then discuss some investigational efforts now in progress. Also, they seek to demonstrate how the therapies currently available can be integrated with surgery and radiation therapy to accomplish more than might be anticipated from chemotherapy alone.

Results: While working to develop better systemic therapies for advanced soft-tissue sarcomas, the integrated use of our best chemotherapy regimens in combination with selected surgical and radiotherapy efforts may provide patients with the best available therapy. Some recent observations involving the use of molgramostim plus chemotherapy have been intriguing.

Conclusions: Progress in the systemic treatment of advanced soft-tissue sarcomas may be gradual, but it is real. Our daily challenge is to be certain that we offer each patient the best available multimodality treatment applicable to his or her clinical situation. Molgramostim should be made available for further study with chemotherapy in controlled clinical trials.

Introduction

With an estimated 6,600 new cases diagnosed in 1997, soft-tissue sarcomas are a diverse group of malignancies with up to 30 distinct subtypes arising from various locations: 50% to 60% from the extremities, 15% to 20% from the trunk, 15% to 25% from the abdomen and retroperitoneum, and 5% to 10% from the head and neck region. Despite this heterogeneity, clinicians historically have tended to consider all soft-tissue sarcomas together and to manage them as if they were a single entity. As we gather greater treatment experience with various soft-tissue sarcomas, we begin to realize the extent of biologic diversity among patients with sarcomatous diseases. With expanding knowledge of these tumors and of host-tumor relationships, we may be better able to tailor effective therapy for these patients. This article reviews the role of systemic therapy for advanced soft-tissue sarcomas, with an emphasis on factors affecting chemotherapy responses, current investigational efforts, and the more effective integration of chemotherapy, radiotherapy, and surgery to improve the outcome of treatment for patients with these diseases.

Conventional Chemotherapy for Advanced Soft-Tissue Sarcomas

The two most active single agents for advanced soft-tissue sarcomas are doxorubicin and ifosfamide with objective regression rates of 15% to 30%. Ifosfamide demonstrates a 7% to 38% response rate among patients who have previously failed a doxorubicin-based regimen. Other active single agents include cyclophosphamide, dacarbazine (DTIC), cisplatin, carboplatin, and etoposide with regression rates of 10% to 20%.

Building on single-agent activity, many combination regimens have been developed including the Southwest Oncology Group’s CYVADIC (cyclophosphamide, vincristine, doxorubicin, and DTIC), Dana-Farber Cancer Institute’s MAID (mesna, doxorubicin, ifosfamide, and DTIC), and Mayo Clinic’s MAP (mitomycin, doxorubicin, and cisplatin). In addition, other small phase II studies -- usually with approximately 50 patients combining doxorubicin and DTIC, doxorubicin and ifosfamide, and ifosfamide and etoposide -- have been used against soft-tissue sarcomas.

The rational combination of the two single most active agents, ifosfamide and doxorubicin, has been used extensively in recent years. Despite higher response rates of 15% to 45% demonstrable with the combination regimens, no combination regimen has yet proven superior to single-agent doxorubicin in promoting survival. In reality, the overall enhancement of survival by any conventional treatment for patients with advanced soft-tissue sarcomas is uncertain, especially when the associated morbidity and toxicity of these aggressive combination regimens is considered.

Factors Affecting Chemotherapy Response

The outcome of chemotherapy for advanced soft-tissue sarcomas may be influenced by multiple factors, including type of sarcoma, tumor burden, tumor grade, metastatic pattern, performance status and, of course, the type and intensity of the treatment itself (Table 1). Certainly, ill and cachectic patients with overwhelming tumor burdens may fail to achieve major benefit from chemotherapy despite our best efforts. Patients with poor performance status or infirmity of old age may have a lower tolerance for chemotherapy and tend to benefit less from chemotherapy than do healthier patients. Several groups have observed that higher-grade sarcomas may respond better to chemotherapy. For instance, in their review of Mayo Clinic studies, van Haelst-Pisani et al demonstrated that higher-grade sarcomas had significantly higher response rates, with regression rates of 55% for grade 4 tumors, 23% for grade 3 tumors, and only 19% for grade 2 tumors. In addition,
independent of grade, estimates of cell proliferation with S-phase fraction have been able to predict response to chemotherapy. Unfortunately, this same characteristic is associated with overall worsening of survival. \textsuperscript{18-20}

<table>
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<tr>
<th>Histologic type of sarcomas</th>
<th>Histologic grade</th>
<th>Performance status</th>
<th>Dose intensity of chemotherapy</th>
<th>Cell proliferation rate (S-phase fraction)</th>
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Table 1. -- Factors Affecting Chemotherapy Response

It is also clear that certain histologic types of soft-tissue sarcomas are more responsive to chemotherapy. Extrasosseous Ewing’s sarcoma and rhabdomyosarcoma are usually quite sensitive to chemotherapy, whereas gastrointestinal stromal sarcomas are notoriously resistant to chemotherapy. In addition, tumors of apparently similar histology may respond differently to chemotherapy depending on their sites of origin. For example, leiomyosarcomas of the gastrointestinal tract (gastrointestinal stromal sarcomas) are much less responsive to chemotherapy than leiomyosarcomas arising from the uterus or from nonvisceral sites. The dominant predilection of these drug-resistant gastrointestinal stromal tumors to metastasize to the liver has led some observers to suggest that all sarcomas metastatic to the liver may be resistant to chemotherapy. \textsuperscript{21}

If conventional chemotherapy is not curative, what can we learn from our experience with the single-agent and combination regimens? These previous studies may provide us with insights into the more effective application of chemotherapy as a part of multimodality treatment for patients with advanced sarcomas, and they may guide our rational therapeutic research efforts.

**Current Investigational Efforts**

Several agents or approaches that are under investigation are listed in Table 2.

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<th>Agent/Approach</th>
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<td>Eadatrexate</td>
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<td>Liposome-encapsulated doxorubicin</td>
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<td>Molgramostim</td>
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<td>Intralional gene therapy with interleukin-2</td>
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Table 2. -- Agents Under Investigation

**Sarcoma-Type Regimen-Specific Treatment**

Due to previously recognized variations in sarcoma responses according to tumor histology, several types of soft-tissue sarcomas are being studied further for sarcoma-type and regimen-specific responsiveness. In an Eastern Cooperative Oncology Group (ECOG) phase III trial comparing doxorubicin with doxorubicin plus ifosfamide and with mitomycin, doxorubicin, and cisplatin, synovial sarcomas appeared most sensitive to doxorubicin and ifosfamide. \textsuperscript{13} To further define this activity, ECOG presently has a phase II trial of doxorubicin and ifosfamide in patients with advanced synovial sarcomas. In a similar fashion, leiomyosarcomas in two ECOG trials appeared somewhat more responsive to the MAP regimen and to the DTIC-doxorubicin regimen than to doxorubicin alone.\textsuperscript{13,22} Following these observations, the Mayo Clinic presently has a phase II trial using DMAP (DTIC combined with MAP) against leiomyosarcomas stratified by site of tumor origin. Eadatrexate also is under study by ECOG subsequent to a report from Memorial Sloan-Kettering Cancer Center suggesting a possible special effectiveness of this agent in patients with malignant fibrous histiocytoma.\textsuperscript{23} Studies of this type may lead to more selective and focused treatment for patients with sarcomas, thus providing greater benefit for those whose tumors are responsive and avoiding unnecessary toxicity for patients with predictably resistant tumors.

**Dose Intensity**

Doxorubicin and ifosfamide both show dose-response relationships. When used at doses of 50 mg/m\textsuperscript{2} or less, doxorubicin has a response rate of approximately 11%. In doses of 60 to 75 mg/m\textsuperscript{2}, doxorubicin has a response rate of 20% to 37%.\textsuperscript{24} Patel et al.\textsuperscript{25} and others have shown a dose-response and schedule-dependent effect of high-dose ifosfamide against soft-tissue sarcomas. To ameliorate dose-limiting myelosuppression, these same M. D. Anderson investigators have successfully intensified doxorubicin-ifosfamide combination regimens with the use of growth factors, most recently adding thrombopoietin.\textsuperscript{26} Although feasible in healthy patients, these intensive regimens are quite toxic, and their long-term benefit in patients with advanced soft-tissue sarcomas remains uncertain. At present, the use of high-dose chemotherapy with autologous stem cell support for advanced soft-tissue sarcomas is experimental, and no major enhancement of survival has been achieved by these activities.\textsuperscript{27}

**New Chemotherapy Agents**

Since patients with metastatic soft-tissue sarcomas are not often cured with the current chemotherapy agents, many investigators continue to study potentially new active agents. New cytotoxic agents that have been tested in phase II trials include pachitaxel, docetaxel, edatrexate, and topotecan. Pachitaxel and docetaxel, taxanes derived from the yew tree, prevent disassociation of the microtubule assembly during mitosis. Pachitaxel in several phase II trials has shown no significant activity.\textsuperscript{28,29} Docetaxel, however, showed promising activity in one phase II study by the European Organization for Research on Treatment of Cancer (EORTC).\textsuperscript{30} The EORTC recently presented follow-up data comparing docetaxel to doxorubicin as first-line therapy for soft-tissue sarcomas and found no responses in those treated with docetaxel.\textsuperscript{31} Docetaxel’s poor activity against soft-tissue sarcomas has also been observed in a phase II study by the Mayo Clinic and the North Central Cancer Treatment Group.\textsuperscript{32} Edatrexate, an analogue of methotrexate that is highly polyglutamated and allows for more effective intracellular retention, has shown some activity in a phase II study against malignant fibrous histiocytoma and is currently undergoing a confirmatory trial by ECOG.\textsuperscript{21} Topotecan is a synthetic camptothecan, a class of drugs that inhibits topoisomerase I. In a phase II study by the London Regional Cancer Centre in Ontario, Canada, topotecan showed low activity in adult soft-tissue sarcomas.\textsuperscript{33} In addition, phase II trials are in development to test the antisarcoma activity of gemcitabine, a nucleoside analogue similar to cytosine arabinoside, in sarcomas.

One of the most interesting new agents currently under study in advanced sarcomas is liposome-encapsulated doxorubicin (LED). This agent appears to be less prone to accumulate in the myocardium, thus less cardiac toxicity is anticipated.\textsuperscript{34} It also may be able to overcome multidrug resistance (MDR)-1-based doxorubicin resistance by avoiding the p-glycoprotein efflux pump.\textsuperscript{35} This agent is currently completing phase II studies in advanced sarcomas. A similar liposomal preparation of daunorubicin also is undergoing phase II studies.
MDR by overexpression of p-glycoprotein is a potentially important mechanism that limits the effectiveness of chemotherapy against soft-tissue sarcomas. Soft-tissue sarcomas are known to have intrinsic and acquired MDR phenotypes. Up to 43% of untreated soft-tissue sarcomas express MDR, and this increases to 52% in those treated with chemotherapy. Attempts to modify anthracycline resistance with cyclosporin have not been very successful when MDR expression has occurred.

**Biologic Response Modifiers/Gene Therapy**

Although interferons have not been effective against soft-tissue sarcomas, the field of biologic therapy for these tumors is quite active. The use of gene therapy in soft-tissue sarcomas is in its infancy. There are multiple approaches to gene therapy, and one recent intraläsional gene therapy study performed by the Arizona Cancer Center using plasmid DNA coding for IL-2 formulated with DMRIE/DOPE, a proprietary cationic lipid mixture, has suggested activity in patients with sarcomas. A multi-institutional study is currently under way to define the extent of this antisarcoma activity. Another GM-CSF-based cellular vaccine is being studied in phase I at the University of Wisconsin.

**Cytokine Augmentation of Cytotoxic Drugs**

Investigators from the Mayo Clinic have recently reported maturing data of a phase I study of antisarcoma regimens (ifosfamide, doxorubicin, and cisplatin ± mitomycin) supported by molgramostim, an *Escheria coli*-derived, nonglycosylated rhGM-CSF. We observed an unexpectedly favorable result, with five of 15 advanced sarcoma patients still surviving after more than four years. The EORTC also performed a phase II study using a dose-intensive ifosfamide and doxorubicin regimen with molgramostim support and demonstrated a 45% response rate (10% complete response). Unfortunately, when the EORTC tried to confirm their apparent doubling of objective regression rates in patients receiving 50% increased doxorubicin doses, molgramostim was not available, so they substituted sargramostim, the yeast-derived, glycosylated rhGM-CSF. The response rate for the dose-intensive regimen with sargramostim was only 21%, thereby suggesting the possibility that the difference in response rates might have been influenced by the cytokine products used. As soon as a supplier of this non-marketed cytokine can be obtained, a phase III trial needs to study the hypothesis that molgramostim, when given subcutaneously in a relatively intensive schedule, might enhance antisarcoma effects initiated by cytotoxic drugs in patients with advanced sarcomas.

**Integration of Chemotherapy, Radiation, and Surgery**

Since patients with advanced soft-tissue sarcomas are in general not cured with single-modality treatments, attempts at combining chemotherapy, radiation, and surgery are necessary. For instance, patients with recurrent/metastatic sarcomas who undergo metastasectomy are at high risk for recurrence, with only 20% to 25% remaining disease-free at five years. It is in this population that trials combining chemotherapy and surgery are important. Patients with metastatic sarcomas who respond to chemotherapy prior to metastasectomy logically might have better survival than those who do not respond to premetastasectomy chemotherapy. Unfortunately, this has not always been borne out in clinical practice. In reviewing the experience of the M. D. Anderson Cancer Center, Lanza et al found that the radiographic response to cyclophosphamide-doxorubicin-dacarbazine chemotherapy prior to pulmonary metastasectomy did not predict survival. The soft tissue and bone sarcoma group of the EORTC is currently studying the value of postmetastasectomy ifosfamide plus doxorubicin chemotherapy in patients undergoing thoracic surgery for metastatic soft-tissue sarcomas.

While the common pattern of pulmonary metastasis from soft-tissue sarcomas has been regularly managed by surgery with or without chemotherapy for at least 25 years, some other advanced disease situations are now amenable to multimodality help as well.

**Illustrative Cases**

**Case No. 1**

A 28-year-old woman noted a left paraspinal mass at the base of her neck early in 1988 with left ulnar paresthesias. Biopsy in late June led to tumor excision in July 1988 of a mesenchymal chondrosarcoma of the left paraspinal muscles with an extension between the interspinous ligaments of T1 and T2. This was followed by external beam irradiation to 50 Gy directed to the tumor bed during the fall of 1988. She remained well for two years, but in early 1991, she developed cough and hemoptysis by March 1994, and prominent dyspnea on exertion by May, leading to sleeve resection of the left upper lobe to eliminate a metastasis that had occluded the left upper lobe bronchus. By September 1994, bilateral pulmonary nodules again had appeared for which she received five monthly treatment cycles, the lung lesions disappeared and the pelvic disease regressed. In late fall 1995, the residual pelvic disease was excised with no gross recurrence when last seen 1.5 years later.

Comments: Conventional treatment for this widely metastatic disease most likely would have been systemic chemotherapy alone, once the lung disease recurred following median sternotomy. Perhaps some physicians would have considered the use of pelvic irradiation for palliative purposes. The decision to use secondary pelvic surgery prior to the last third of her six cycles of ifosfamide and doxorubicin chemotherapy did not predict survival. The soft tissue and bone sarcoma group of the EORTC is currently studying the value of postmetastasectomy ifosfamide plus doxorubicin chemotherapy in patients undergoing thoracic surgery for metastatic soft-tissue sarcomas.

**Case No. 2**

A 32-year-old woman noted a left paraspinal mass at the base of her neck early in 1988 with left ulnar paresthesias. Biopsy in late June led to tumor excision in July 1988 of a mesenchymal chondrosarcoma of the left paraspinal muscles with an extension between the interspinous ligaments of T1 and T2. This was followed by external beam irradiation to 50 Gy directed to the tumor bed during the fall of 1988. She remained well for two years, but in early 1991, she developed cough and tightness in her left thorax. Bronchoscopy in July 1991 revealed left hilar tumor penetrating the left upper lobe bronchus and obstructing the left lower lobe bronchus, which on biopsy showed metastatic mesenchymal chondrosarcoma. She then received ifosfamide, doxorubicin, and dacarbazine with G-CSF (filgrastim) for 10 months at her home hospital with grossly complete tumor regression. Within three months, however, a left lower lobe mass had appeared. This seemed to not have responded to therapy prior to the last third of her six cycle systemic treatment would probably not be conventional at most institutions, and some might consider this unnecessarily aggressive treatment in a patient apparently destined to die of her metastatic cancer. However, we have recently observed more successes than might be expected using therapy of this sort, especially in relation to IMAP plus molgramostim.
Comments: This case reminds us of the cartoon depicting the frog who absolutely refuses to be swallowed by the heron -- "Don’t ever give up!" Chemotherapy was a necessary part but by no means a sufficient solution to this problem. Without chemotherapy-induced regression of the (categorically incurable?) hilar metastatic disease in 1992, life might have ended five years ago. Are the six thoracotomies considered extreme therapy? The selective application of surgery and irradiation effectively integrated with systemic therapy may at times permit us to accomplish more than ordinarily could be anticipated.

Conclusions

As the quality of our chemotherapeutic efforts continues to improve, the effect on these multimodality activities could be surprising. However, if we are to obtain the best possible therapy for our patients, the integrated application of surgery and radiation therapy to the problems of advanced soft-tissue sarcomas will be required for the foreseeable future. Although the sequence of treatments planned must be individually selected according to the problems facing each patient, our current approach to advanced soft-tissue sarcomas tends toward initiating treatment with chemotherapy to achieve as much overall disease control as possible before applying more focused therapy with irradiation and surgery.

References


From the Division of Medical Oncology at the Mayo Clinic, Rochester, Minn.

Address reprint requests to Dr Okano at the Division of Medical Oncology, Mayo Clinic, 200 First Street SW, Rochester, MN 55905.