Treatment of Advanced Soft Tissue Sarcoma: Conventional Agents and Promising New Drugs

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Sarcoma, chemotherapy, targeted therapies, GIST

Abstract
Effective treatment of advanced soft tissue sarcomas remains challenging, despite more than 30 years of clinical trials with conventional chemotherapy. Although some agents display modest efficacy against soft tissue sarcomas, modifications in the doses and combinations of therapies have not consistently led to significant improvements in response rates or concomitant increase in overall survival. Novel therapies designed to inhibit defined molecular alterations, as exemplified by the use of imatinib in gastrointestinal stromal tumors, have revolutionized the approach to the treatment of sarcomas. As more underlying genetic mechanisms are uncovered, new agents designed to target these lesions will lead to more specific, less toxic, and more effective therapies. (JNCCN 2007;5:401–410)

Soft tissue sarcomas are a heterogeneous group of malignant tumors that share a common mesenchymal origin. These diseases can be subclassified into more than 50 different types that vary in their location at presentation (extremities, 50%; soft tissues of trunk, abdomen, and retroperitoneum, 40%; and head and neck, 10%), histologic grade, rate of growth, and risk for metastatic disease. Although surgical management of localized disease remains the mainstay of therapy, these tumors can be metastatic at presentation or can recur systemically, at which time chemotherapy is considered. The low prevalence of each subtype has limited the ability to analyze the effectiveness of therapies, and most reports describe single-arm phase II studies, combine multiple subtypes of sarcoma, or are case series of small numbers of patients. Despite these limitations, several antineoplastic chemotherapeutic agents have emerged as having efficacy against sarcomas in general, although response rates overall are low and can vary greatly when individual histotypes are considered. This article describes drugs that are commonly used to treat advanced sarcomas and highlights regimens that seem particularly active in certain subsets. With an increasing understanding of the molecular changes underlying sarcoma formation, novel therapies designed to target these pathways are in development. These new agents are also discussed.

Commonly Used Single-Agent Chemotherapeutic Drugs for Advanced Sarcoma
Doxorubicin and Pegylated Liposomal Doxorubicin
Doxorubicin has been an integral component of sarcoma chemotherapy since its introduction in the 1970s, when single-agent response rates of 20% to 25% were reported. Over the past 30 years, the efficacy of doxorubicin has continued to be studied both as a single agent and in combination with other chemotherapeutic agents. Remarkably, the single-agent activity of doxorubicin in treating advanced sarcoma has remained in the same range as initially reported, despite earlier technologic limitations in accurately determining tumor sizes. For example, one arm of a prospective, randomized trial comparing single-agent doxorubicin to combination therapies documented a 23%
response rate in 263 patients treated with doxorubicin (75 mg/m² every 3 weeks), with only 4% of patients experiencing a complete response.2 Histologies of responding diseases were not delineated in this report. In another phase III study, doxorubicin (75 mg/m² every 3 weeks) was administered to 43 patients with metastatic sarcoma and compared with docetaxel (see below for discussion of docetaxel results).3 Partial responses were seen in 30% of patients undergoing initial chemotherapy and 13% undergoing second-line treatment. An additional 37% and 50% experienced disease stabilization in first- and second-line treatment, respectively. Patients who experienced response included 5 of 7 (71%) with liposarcoma and 4 of 14 (29%) with leiomyosarcoma. Randomized or serial studies of alterations in the schedule of doxorubicin dosing (70 mg/m² every 3 weeks vs. 60 mg/m² over 3 days followed by 15 mg/m² weekly)4 or the dosage (50 vs. 75 mg/m² every 3 weeks, or 75 vs. 90 mg/m², all with ifosfamide)5,6 did not identify an improved response rate in either arm.

The antitumor activity of pegylated liposomal doxorubicin and concomitant side effects compared with those of standard doxorubicin were measured by the European Organisation for Research and Treatment of Cancer (EORTC) Soft Tissue and Bone Sarcoma Group in a phase II study of 94 patients with advanced soft tissue sarcoma.7 Patients were randomized to receive either pegylated liposomal doxorubicin (50 mg/m² every 4 weeks) or doxorubicin (75 mg/m² every 3 weeks) as first-line therapy. Leiomyosarcomas, angiosarcomas, and synovial sarcomas were the most common histotypes. Myelosuppression, alopecia, and decreased ventricular function were less frequent and less severe in patients treated with the pegylated liposomal formulation and palmar–plantar dysesthesia was more common. Response rates were similar, with approximately 10% of patients in each arm experiencing a complete or partial response, and 30% to 40% experiencing disease stabilization. Median times to progression and estimated overall survival were 65 and 320 days, respectively, for pegylated liposomal doxorubicin and 82 and 246 days, respectively, for doxorubicin. Other studies of pegylated liposomal doxorubicin in sarcomas have found similar8 or poorer9 response rates.

The response rates after treatment with doxorubicin in the EORTC study were markedly lower than previous studies by the same group and other investigators. This variability in observed response rates may be partly caused by changes in techniques used to assess tumor sizes but more likely reflects the heterogeneity of tumor histotypes enrolled in these studies and their inherent differences in chemosensitivity.

Dacarbazine and Temozolomide

Dacarbazine (5-[[dimethyltriazenolimidazole-4-carboxamide or DTIC) was similarly shown to have antitumor activity in studies reported in the 1970s. Single-agent activity with an overall response rate of 17% was observed in adult patients with metastatic sarcomas in a trial conducted by the Southwest Oncology Group and the M. D. Anderson Hospital and Tumor Institute.8,9,11 The efficacy of temozolomide, an oral prodrug of 5-3-methyl-1-triazenolimidazole-4-carboxamide (MTIC; the active metabolite of DTIC), has also been studied in patients with advanced sarcomas. A phase II study by the EORTC Soft Tissue and Bone Sarcoma Group reported only 1 response in 31 patients with advanced soft tissue sarcoma treated with temozolomide at 750 mg/m² divided over 5 days, for a response rate of 3.3%.11 Median time to progression and median overall survival were 8 weeks and 23 weeks, respectively.

In a second study, an overall objective response rate of 8% was observed in 25 patients treated on a schedule of twice-daily 200 mg/m² doses for 5 days followed by 9 doses of 90 mg/m², in a 28-day cycle.12 Clinical benefit was seen only in patients with leiomyosarcoma; of the 11 patients with this disease, 2 experienced partial responses, 2 experienced mixed responses, and 3 experienced stable disease for more than 6 months. Median progression-free and overall survival times were 2.0 and 13.2 months, respectively. A third study treated patients with 85 mg/m² daily for 21 days, followed by 1 week without treatment, and reported 1 complete response (in a patient with malignant fibrous histiocytoma) and 1 partial response (leiomyosarcoma) among 39 patients, with an overall response rate of 5%.12 Disease stabilization was observed in 33% of patients. Median time to progression was 3.3 months, and median overall survival was 11 months. The Spanish Group for Research on Sarcomas investigated the benefits of continuous dosing at 75 or 100 mg/m² in 6-week cycles, and observed 7 partial responses among 45 patients, for an overall response rate of 15.5%, including 5 of 11 patients with uterine leiomyosarcoma.13 Despite the continual dosing scheme, the median time to progression and
median overall survival remained 2.2 and 8.1 months, respectively.

**Ifosfamide**

Use of ifosfamide for treating advanced soft tissue sarcomas was initially studied in the 1980s. A phase II study involving 42 patients treated with 5 or 8 g/m² as a 24-hour infusion every 3 weeks, with mesna uroprotection, observed 6 complete responses (15%) and 9 partial responses (23%). Toxicity included severe nausea and vomiting; myelosuppression; renal tubular defects, including fatal nephrotoxicity; and treatment-related somnolence. A similar benefit was observed in a phase II study of ifosfamide (8–10 g/m² divided over 4 days) in previously treated patients: 10 of 28 patients (36%) experienced a partial response with myelosuppression, neurotoxicity, and nephrotoxicity as the major side effects. Response rates to ifosfamide (5 g/m²) were superior to cyclophosphamide (1.5 g/m²) in a randomized phase II study comparing 24-hour infusions every 3 weeks, with more responses after treatment with ifosfamide (18% of 68 patients) than with cyclophosphamide (7.5% of 67 patients). Both agents had higher response rates when used as first-line treatments (25% and 13%, respectively).

Administered doses of ifosfamide vary greatly in different trials. Sequential phase II studies at the M. D. Anderson Cancer Center examined response rates in relation to increasing doses of ifosfamide. At 6 g/m², the overall response rate was 10%, and at 10 g/m² a response rate of 21% was observed, suggesting a dose–response relationship, although these studies were not designed for direct comparison. High-dose ifosfamide (14 g/m²) as a 74-hour continuous infusion was administered to 37 patients with soft tissue sarcoma in a phase II study and as bolus infusion divided over 4 days to 9 patients with soft tissue sarcoma in a pilot study. Overall response rates of 19% and 45% were observed for the infusion and bolus administration schedules, respectively. All patients received mesna uroprotection and growth factor support. Peripheral neuropathy and renal, central nervous system, and cardiac toxicity were the major severe side effects. In a randomized phase II study, the EORTC Soft Tissue and Bone Sarcoma Group investigated the effects of ifosfamide administered as a 24-hour infusion of 5 g/m² or as 3 days of bolus infusions of 3 g/m²/d in patients with advanced soft tissue sarcomas. As a first-line agent, the 5 g/m² 24-hour infusion yielded a response rate of 10%, whereas the response rate was 25% in the 3 g/m² × 3-day bolus infusion arm. For second-line treatment, response rates were similar at 6% and 8%, respectively. Although this study was not intended to directly compare the arms, median time to progression and median overall survival were not significantly different.

In another randomized phase II study, the effects of doxorubicin in combination with 6 or 12 g/m² of ifosfamide were assessed in patients with localized or metastatic soft tissue sarcoma. Of the 25 patients with metastatic disease, 3 of 13 (23%) treated with 6 g/m² obtained an objective response (including 2 complete responses), as did 3 of 12 (25%) treated at 12 g/m² (with 1 complete response). No significant difference in survival was observed.

**Gemcitabine**

Several phase II studies of patients with advanced sarcomas have examined the antitumor activity of single-agent gemcitabine administered at 1000 to 1250 mg/m² weekly × 3 weeks in 4-week cycles. Response rates have ranged from 4% to 18%, with 1 to 3 responses per trial, typically occurring in patients with uterine leiomyosarcoma. Disease stability has been observed in a slightly larger percentage of patients.

One study examined the use of gemcitabine, 1000 mg/m² (infusion rate not indicated), administered weekly for 7 weeks followed by 1 week of rest and then maintenance therapy with the same dose administered weekly for 3 weeks every 28 days. A total of 18 patients with previously treated advanced sarcomas were enrolled, and of these, 10 had bone sarcomas. Three patients did not complete the induction cycle because of tumor progression, and 6 patients experienced no objective benefit from induction therapy. Of the original 18 patients, 1 with uterine leiomyosarcoma experienced a partial response, 1 with angiosarcoma of the scalp experienced a minor response, and 6 with chondrosarcoma or osteosarcoma experienced stabilization of previously growing disease. The objective response rate was 5.5% but, including patients with stabilization, 44% experienced disease-control. Median time to progression was 27 weeks, and overall the treatment was well-tolerated.

A similarly designed study also used gemcitabine at 1000 mg/m², infused over 30 minutes, weekly for 7 weeks of 8, then weekly for 3 weeks every 28 days. This 2-arm study involved 17 patients with gastrointestinal leiomyosarcoma and 39 patients with other...
soft tissue sarcomas. The former tumors likely included typically chemoresistant gastrointestinal stromal tumors (GIST), but no responses were seen in this population and accrual was stopped. Of the remaining 39 patients, 7 objective responses were observed (18%), including 3 patients with uterine leiomyosarcoma, 1 patient with leiomyosarcoma of an extremity, and 1 patient each with angiosarcoma, malignant fibrous histiocytoma, and an unclassified sarcoma. Six patients experienced grade 3 or 4 myelosuppression, and median time to progression for all patients was 3 months.

The Eastern Cooperative Oncology Group (ECOG) treated 25 patients with previously untreated advanced sarcomas with gemcitabine 1250 mg/m² as a 30-minute infusion weekly for 3 weeks every 28 days. One patient with an epitheliod sarcoma obtained a partial response, yielding a response rate of 4%. All patients developed grade 3 or 4 toxicity, most commonly myelosuppression.

In a phase II study, 18 patients with advanced soft tissue sarcoma were treated with a lower dose of gemcitabine (200 mg/m²) with a longer duration of infusion (360 minutes), theoretically increasing the intracellular exposure to active drug. Patients were treated weekly for 3 weeks on a 28-day cycle. Three of 18 patients experienced a partial response, and 6 experienced stable disease for 306 months. Median survival was 8 months. Six patients experienced transient grade 3 nonhematologic toxicity, and 5 patients experienced grade 3 or 4 myelosuppression.

**Docetaxel**

Effects of docetaxel as a first- or second-line agent in treating metastatic sarcomas have been studied in several trials. In a study of 29 patients with advanced sarcoma, docetaxel 100 mg/m² every 3 weeks resulted in 5 partial responses (17%), with severe neutropenia as the major toxicity. However, a second study using the same dose of docetaxel in 17 patients observed only 1 partial response (6%) in a patient with metastatic uterine leiomyosarcoma. Similarly, no responses to docetaxel were seen in 43 patients enrolled in a randomized trial comparing docetaxel with doxorubicin as first- or second-line therapy. Leiomyosarcoma, liposarcoma, and synovial sarcoma were the most common diagnoses in this study. In a study of patients with advanced sarcoma refractory to prior treatment with anthracyclines and ifosfamide, 27 patients were treated with docetaxel 100 mg/m² every 3 weeks or, if this dose was poorly tolerated, with docetaxel 40 mg/m² weekly. Partial responses were seen in 4 patients (15%), and 4 patients (15%) experienced disease stabilization. Median progression-free and overall survival remained dismal, at 2.7 and 7.7 months, respectively.

**Combination Chemotherapy**

**Doxorubicin and DTIC**

Based on the early descriptions of responses to single-agent doxorubicin and DTIC, these agents were used in combination in the 1970s with a reported response rate of 42%. Further studies confirmed their enhanced activity when used together. The Gynecologic Oncology Group reported a trend toward improved response rates in patients with uterine sarcomas treated with doxorubicin and DTIC compared with doxorubicin alone (24% vs. 16%, \( P > .05 \)). In a randomized study performed by the ECOG, patients with soft tissue sarcoma were randomized to 1 of 2 different schedules of doxorubicin or to doxorubicin 60 mg/m² once every 3 weeks in combination with DTIC 1250 mg/m² divided over 5 days. More patients treated with combination doxorubicin and DTIC experienced a response than those treated with single-agent doxorubicin (30% vs. 17%, respectively). Response rates were greatest for patients with leiomyosarcoma undergoing combination therapy (44%). Severe toxicities, in particular nausea/vomiting and myelosuppression, were greater with combination therapy than with single-agent doxorubicin. Median survival time was 8 months in all treatment groups, regardless of response rates.

**Doxorubicin, Ifosfamide, and DTIC**

In a phase II trial, 105 previously untreated patients with sarcoma received doxorubicin (60 mg/m²), ifosfamide (7500 mg/m²), and DTIC (900 mg/m²) with mesna uroprotection (MAID) administered over 72 hours by continuous infusion. The overall response rate was 47%, including 10% of patients who experienced complete responses. Median time to progression was 10 months and median survival was 16 months. A randomized trial by SWOG and CALGB studied doxorubicin, ifosfamide, and DTIC in combination versus doxorubicin and DTIC. Patients receiving all three drugs experienced higher response rates (32% vs. 17%) and longer times to progression.
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(6 vs. 4 months) than patients receiving doxorubicin and DTIC. However, a small survival advantage was seen for the 2-drug regimen (13 vs. 12 months, \( P < .05 \) but not statistically significant by multivariate analysis).

**Doxorubicin and Ifosfamide**
The combination of doxorubicin and ifosfamide with mesna (AIM) has been used in several studies. A phase II multi-institutional investigation used doxorubicin 60 mg/m\(^2\) by continuous push and ifosfamide 5 g/m\(^2\) by 24-hour infusion.\(^2\) Objective remissions were observed in 15 of 42 patients (36%), including 3 complete remissions. Median survival was 8 months. In serial studies at the M. D. Anderson Cancer Center that administered doxorubicin at either 75 or 90 mg/m\(^2\) as a 72-hour continuous infusion in combination with ifosfamide 2 g/m\(^2\)/d \( \times 5 \) days,\(^3\) 21 of 33 evaluable patients (64%) experienced response, including 3 complete responses. Febrile neutropenia commonly occurred, whereas central nervous system and fatal cardiac toxicities were rare.

A 3-arm randomized phase III trial, doxorubicin combined with ifosfamide was compared with doxorubicin alone and the combination of cyclophosphamide, vincristine, doxorubicin, and DTIC (CYVADIC).\(^2\) The overall response rate was 26% in 605 evaluable patients. No statistically significant difference was observed among the arms for response rate or median overall survival.

**Gemcitabine and Docetaxel**
The combination of gemcitabine (900 mg/m\(^2\) as a 90-min infusion, days 1 and 8) and docetaxel (100 mg/m\(^2\)) on day 8 was administered to patients with unresectable leiomyosarcoma in 21-day cycles.\(^4\) Patients who had previously been treated with radiation therapy received reduced doses of 675 and 75 mg/m\(^2\), respectively. Sixteen of 34 patients had previously received doxorubicin, with or without ifosfamide. Most patients (85%) had uterine leiomyosarcoma. Three complete responses and 15 partial responses were observed, with an overall response rate of 53%. Responses were seen in 50% of the 16 women previously treated with doxorubicin. The median progression-free survival was 5.6 months, and median overall survival was 17.9 months. Major toxicities included myelosuppression, dyspnea, diarrhea, sensory neuropathy, and fatigue.

A randomized, multi-institutional phase III study compared gemcitabine (1200 mg/m\(^2\)/days 1 and 8) with gemcitabine (900 mg/m\(^2\)/days 1 and 8) in combination with docetaxel (100 mg/m\(^2\)/day 8) administered in 21-day cycles to patients with metastatic soft tissue sarcomas.\(^5\) Using a primary outcome of tumor response (complete response, partial response, or stable disease for more than 24 weeks), 27% of 49 patients treated with gemcitabine alone and 32% of 73 patients treated with the combination responded. Patients treated with gemcitabine and docetaxel were more likely to experience a radiologic response (16% vs. 10%; \( P = .15 \)), obtain longer progression-free survival (6.2 vs. 2.6 months), and have longer overall survival (18 vs. 11.2 months), but experienced greater toxicity, necessitating discontinuation from treatment (\( P < .01 \)).

A recent retrospective analysis of combination fixed-dose-rate gemcitabine (900 mg/m\(^2\)/day over 90 min, days 1 and 8) and docetaxel (100 mg/m\(^2\)/day 8) every 21 days reported an overall response rate of 18% in 133 patients.\(^6\) Compared with patients with other histotypes, those with leiomyosarcomas experienced higher response rates (24% vs. 10%, \( P = .06 \)) and longer overall survival. No significant difference in response rates was observed in uterine sarcomas compared with other histotypes.

In summary, various conventional chemotherapeutic agents have modest activity against advanced soft tissue sarcomas, and although trials have occasionally shown an increased response rate with higher doses or combination therapy, this has been at the expense of increased toxicity and without a clear improvement in overall survival. For some patients, however, a partial response may help alleviate symptoms or complications of local tumor growth even if the treatment regimen does not extend survival. The appropriate chemotherapeutic regimen and timing of treatment should be decided on an individualized basis.

The other major limitation to these studies is that patients with many different types of mesenchymal tumors were pooled together in treatment arms. What may be an effective therapy for one sarcoma may not necessarily be effective for another, much like different epithelial carcinomas respond differently to the same treatment. Sarcomas, however, are diseases that can be difficult to classify accurately and are of low prevalence, making accrual of large numbers of patients both technically and practically difficult. Nonetheless, expert histopathologic diagnosis combined with an improved molecular understanding of sarcoma biology can lead to dramatic improvements.
in sarcoma treatment, as has been the case for GIST. Although recent treatment advances in GIST may reflect a unique confluence of basic science discovery, drug design, and clinical trial design and execution, these discoveries have provided a prototypical model for the development and implementation of novel and effective anticancer therapy.

**Imatinib and Sunitinib in GIST**

Many early studies of chemotherapy for soft tissue sarcoma noted that gastrointestinal leiomyosarcomas were resistant to treatment. In retrospect, many of these tumors were likely GIST, characterized by expression of CD117, the c-KIT protein. An understanding of the common oncogenic molecular mechanisms of this disease, namely, activating mutations in the genes encoding the c-KIT or platelet-derived growth factor receptor (PDGFR)-A tyrosine kinases in approximately 90% and 5% of GIST, respectively, has led to the development of highly effective, well-tolerated therapies that specifically inhibit these enzymes and consequently reduce disease burden and improve patient survival.

Two agents, imatinib mesylate and sunitinibmalate, are approved by the U.S. Food and Drug Administration for treating metastatic or unresectable GIST; imatinib as a first-line agent, and sunitinib in cases of intolerance of or resistance to imatinib. Imatinib is a potent inhibitor of the c-KIT, ABL, and PDGFR tyrosine kinases, whereas sunitinib displays a broader range of activity, inhibiting c-KIT, vascular endothelial growth factor receptor (VEGFR), PDGFR, RET, FLT3, and other kinases. As a first-line agent in a phase II study, treatment with imatinib resulted in sustained partial responses in 54% of patients and stable disease in 28%. Responses to treatment correlated with the underlying mutation: 83% of patients with tumors harboring exon 11 KIT mutations showed a partial response compared with only 48% of patients with exon 9 KIT mutations or no detectable mutation, and 0% of patients with PDGFR-A mutations.

Two large randomized studies have examined the effect of imatinib dose on response and progression-free survival. A phase III study performed by the EORTC Soft Tissue and Bone Sarcoma Group, the Italian Sarcoma Group, and the Australasian Gastrointestinal Trials Group randomized 946 patients with advanced GIST to 400 mg of imatinib once or twice daily. At progression, patients assigned to the once-daily regimen were permitted to cross over. No differences were seen in the rates of complete (5%) or partial (47%) responses or disease stabilization (32%). Toxicity requiring dose reduction was more commonly seen in the twice-daily arm (60% vs. 16%). At publication, progression-free survival was greater in the twice-daily arm (56% vs. 50% at a median follow-up of 760 days; hazard ratio 0.82, \( P = .026 \)), but no difference occurred in the overall survival estimates (once daily, 85% at 1 year and 69% at 2 years; twice daily, 86% at 1 year and 74% at 2 years). At a median follow-up of 768 days in a similarly designed North American Sarcoma Intergroup study, however, progression-free survival rates at 2 years were 50% and 53% (\( P > .05 \)) and estimated 2-year survival rates were 78% and 73% for 400-mg and 800-mg arms, respectively.

Despite initial disease control in most patients, resistance to imatinib may develop as a consequence of disease. The intra-patient heterogeneity of response duration suggests the clonal expression of secondary mutations, and novel mutations of KIT were identified in tumors from 44% to 67% of patients with secondary resistance. These mutations were not detectable in the original lesion before imatinib treatment in either the ATP-binding pocket or the kinase activation loop, and conferred enhanced in vitro resistance to imatinib.

After progression of disease on imatinib therapy, one treatment option is to increase the dose. Patients in the North American Sarcoma Intergroup phase III study who experienced disease progression on 400 mg of imatinib and then crossed over to 800 mg daily experienced partial responses (7%) or disease stabilization (29%) at the higher dose. Alternatively, sunitinib has also proved to be an effective treatment for imatinib-resistant GIST. In a phase I/II study, treatment with sunitinib resulted in disease control in approximately 80% of patients. A phase III placebo-controlled study of sunitinib in patients with GIST who were resistant to or intolerant of prior imatinib therapy showed significantly improved time to progression (27 vs. 6 weeks) and overall survival (hazard ratio 0.49; median survival not yet reached in either arm), favoring sunitinib. Interestingly, estimated time to progression was significantly longer for tumors harboring an exon 9 or no detectable KIT mutation, compared with an exon 11 mutation, in contrast to the effect noted with first-line imatinib.

Imatinib also has been shown to be effective against 2 other sarcomas: dermatofibrosarcoma protuberans (DFSPs) and desmoid tumors (aggressive...
fibromatosis.\textsuperscript{52–55} DFSPs typically contain translocations of the gene encoding platelet-derived growth factor (PDGF) beta to the control of the collagen alpha 1 promoter, leading to dysregulated expression of PDGF beta and stimulation of PDGFR. Treatment of DFSP cell lines with imatinib led to growth inhibition and induction of apoptosis.\textsuperscript{53} Clinical responses have been reported in patients with advanced or metastatic DFSP treated with daily doses of 400 or 800 mg of imatinib.\textsuperscript{54} Similarly, patients with desmoid tumors may experience a partial response or disease stability during treatment with imatinib 800 mg daily, potentially through inhibition of PDGFR.\textsuperscript{52,53}

**Promising New Agents**

**Tyrosine Kinase Inhibitors**

Other drugs that inhibit c-KIT and other tyrosine kinases are currently in clinical trials for the treatment of GIST and other sarcomas. These include nilotinib (AMN 107), dasatinib, and AMG 706. Nilotinib is a second-generation kinase inhibitor designed to inhibit c-KIT, PDGFR, and ABL tyrosine kinases. In a phase I study of patients with imatinib-refractory GIST, nilotinib alone or in combination with escalating doses of imatinib was well tolerated.\textsuperscript{56} Initial data with short follow-up in 18 patients showed progressive disease in 3 patients and disease stabilization in the remaining 15. Dasatinib, which is approved for use in imatinib-refractory chronic myelogenous leukemia, is being tested in a phase I study in patients with GIST and other solid tumors. In this dose-escalation study, no responses have been observed, but disease stability has allowed for more than 3 monthly cycles of treatment in 4 patients with GIST and 3 patients with other sarcomas.\textsuperscript{57} AMG 706 is an orally administered inhibitor of c-KIT, PDGFR, VEGFR, and RET. A phase II study of 138 patients with GIST who had previously progressed on imatinib therapy found that AMG 706 induced stable disease for more than 22 weeks in 25% of patients.\textsuperscript{58} Common adverse events included diarrhea, hypertension, fatigue, headache, and nausea. The molecular genotypes of tumors responding to any of these treatments have not yet been described. Although none of these investigational agents has shown the same degree of success as imatinib or sunitinib in treating GIST, they represent the interest of pharmaceutical companies in developing next-generation oral kinase inhibitors and reflect the beginning of a larger pipeline soon to enter clinical trials.

**mTOR Inhibitors**

The phosphotidylinositol 3-kinase (PI3K)/AKT/mTOR signaling pathway has been implicated as a contributor to the pathogenesis of various human cancers, including sarcomas. Inhibitors of mTOR, derivatives of rapamycin, have recently been tested in the treatment of GIST and other sarcomas. Everolimus (RAD-001), an orally administered mTOR inhibitor, was combined with imatinib in a phase I/II study of patients with GIST refractory to imatinib alone.\textsuperscript{59} Stable disease greater than 4 months was observed in 8 of 31 patients. Two patients developed a partial response and 9 withdrew from the study because of adverse events, including stomatitis, thrombocytopenia, and gastritis. In a phase II study, temsirolimus (CCI-779) was administered to 41 patients with advanced soft tissue sarcoma as a weekly infusion in 4-week cycles.\textsuperscript{60} More than 40% of patients experienced grade 3 or 4 toxicity, including myelosuppression, hyperglycemia, fatigue, nausea and vomiting, and stomatitis. A partial response was seen in one patient with a fibrosarcoma, and median time to progression was 2 months.

A third mTOR inhibitor, AP23573, was found in a phase I dose-escalation trial to induce disease stability in a patient with metastatic sarcoma,\textsuperscript{61} prompting a phase II study of 216 patients treated with 12.5 mg/d intravenously for 5 days every 2 weeks.\textsuperscript{62} The primary end point of clinical benefit response, defined as complete or partial response or stable disease greater than 16 weeks, was experienced by 28% of patients, although only 5 patients experienced partial responses. Stomatitis, fatigue, and rashes were common toxicities, but grade 3 to 4 toxicities were rarely reported. Median progression-free survival was 15 weeks.

**Trabectedin**

Trabectedin (ET-743) is a compound derived from the sea squirt that has anticancer effects believed to be mediated by its ability to bind to the minor groove of DNA and modulate the transcription-coupled nucleotide excision repair system. Several phase II studies have examined the effect of treatment with trabectedin in patients with soft tissue sarcomas. No apparent benefit was seen in 28 patients with advanced GIST treated with trabectedin 1.5 mg/m\textsuperscript{2} as a 24-hour continuous infusion.\textsuperscript{63} Nine patients (33%) experienced stable disease, but median time to progression...
and overall survival were 51 and 589 days, respectively. Two phase II studies have examined the effects of trabectedin in patients with soft tissue sarcoma refractory to prior therapy. One study treated 36 patients with trabectedin 1.5 mg/m² as a 24-hour infusion every 3 weeks and showed 1 complete response, 2 partial responses, and 2 minor responses, for an overall clinical benefit of 14%. The median time to progression and overall survival were 1.7 and 12.1 months, respectively. A larger phase II study by the EORTC Soft Tissue and Bone Sarcoma Group similarly treated 104 patients and observed 8% partial responses and 26% disease stabilization for more than 6 months. Disease control (response or stabilization) was achieved in 56% of patients with leiomyosarcoma and 61% of patients with synovial sarcoma. Median time to progression was 105 days and median overall survival was 9.2 months. Toxicity in both trials included neutropenia and reversible transaminitis.

**HSP90 Inhibitors**

The molecular chaperone HSP90 assists in the normal folding of proteins during protein synthesis and seems to be particularly important in stabilizing mutated or chimeric proteins, which appear to have disadvantageous thermodynamic properties. Mutations and translocations commonly occur in subsets of soft tissue sarcomas, and inhibitors of HSP90 are actively undergoing preclinical and clinical testing. The stability of the mutated c-KIT protein, for example, is dependent on HSP90 function, and treatment of GIST cells with the HSP90 inhibitor 17-allylamino-17-demethoxygeldanamycin (17-AAG) led to rapid and potent decrease in KIT protein levels and signaling. The use of 17-AAG in the clinic has been limited by its insolubility and the need for toxic solvents to allow administration to patients. A water-soluble 17-AAG prodrug, IPI-504, is currently in clinical testing for patients with GIST. Results of this ongoing phase I study suggest that IPI-504 is well tolerated. No computed tomographic responses were observed, but 7 of 14 patients experienced disease stability, and decreases in tumor fluorodeoxyglucose avidity were noted on positron emission tomography imaging in 6 of 14 patients. Reports of sensitivity of other sarcoma model systems to HSP90 inhibition make this pathway an attractive target for future clinical trials.

**Summary**

Effective therapies for most advanced soft tissue sarcomas remain elusive. Alterations in doses and combinations of conventional chemotherapy have not led to meaningful increases in response rates, because this often occurs at the expense of substantial toxicity and no significant increase in overall survival has been observed. Many studies have been hindered by the heterogeneity of tumor types included, and the rare nature of sarcomas make disease-specific trials difficult to perform. With therapies targeted to defining molecular alterations in specific disease subtypes, however, dramatic improvements in patient outcomes can be obtained, as recent experience in treating GIST has shown. The example of GIST is very encouraging, but whether similar essential oncogenic events can be effectively targeted in other sarcoma subtypes remains to be seen. More than 40% of sarcoma subtypes contain characteristic chromosomal translocations or amplifications. Although many translocated genes have been identified, they are either of unknown function or encode transcription factors that are notoriously difficult to pharmacologically target. Critical to the future development of novel, effective therapies for advanced sarcomas is a more thorough understanding of the molecular events underlying sarcoma development, creation of representative cell line and animal models, and continued interest of pharmaceutical corporations in developing agents active against these diseases.

**References**

5. Le Cesne A, Judson I, Crowther D, et al. Randomized phase III study comparing conventional-dose doxorubicin plus ifosfamide versus high-dose doxorubicin plus ifosfamide plus recombinant human...
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35. Maki RG, Hensley ML, Warthen JK, et al. A SARC multicenter phase III study of gemcitabine (G) vs. gemcitabine and docetaxel (G+D) in patients (pts) with metastatic soft tissue sarcomas (STS) [abstract]. J Clin Oncol 2006;24(suppl 1): Abstract 9514.


61. Mita MM, Rowinsky EK, Goldston ML, et al. Phase I, pharmacokinetic (PK), and pharmacodynamic (PD) study of AP23573, an mTOR inhibitor, administered IV daily X 5 every other week in patients (pts) with refractory or advanced malignancies [abstract]. J Clin Oncol 2004;22(suppl): Abstract 3076b.


