



Dorothy Fox. *Cowboy*. Watercolor, 22" × 30".

The therapeutic potential of directed tyrosine kinase inhibitors in sarcoma patients is reviewed.

Therapeutic Potential of Directed Tyrosine Kinase Inhibitor Therapy in Sarcomas

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Background: Sarcomas are rare mesenchymally derived tumors for which there are limited treatment options. This paper discusses the current therapeutic potential of directed tyrosine kinase inhibitors (TKIs) in sarcoma.

Methods: The authors review antibody-based strategies and small molecular inhibitors of TKIs, with specific emphasis placed on the potential use of these targeted agents as therapeutic options for the treatment of sarcomas that are not gastrointestinal stromal tumors.

Results: Many TKs have been shown to be mutated or overexpressed in human sarcoma tumors and cell lines and may serve as potential targets for promising new sarcoma therapies. Furthermore, the novel mechanism of targeting TKs may complement the antitumor activity of existing sarcoma treatment options.

Conclusions: TKIs such as imatinib, sunitinib, and sorafenib are promising new therapeutic options for the management of patients with soft tissue sarcoma.

Introduction

Sarcomas are rare and diverse malignancies that arise from mesenchymally derived connective tissues. They are a heterogeneous group of malignancies with more than 50 different types that vary in their clinical presentation, disease course, histology grade, growth rate,

and metastatic potential. With approximately 12,000 new cases diagnosed each year nationwide, sarcomas account for a small fraction of all newly diagnosed cancers in the United States.¹ Sarcomas, however, represent more than 20% of newly diagnosed pediatric malignancies and are among the cancers that confer the greatest risk of mortality and morbidity in children and young adults.²⁻⁷

Surgical management remains the mainstay of treatment of localized disease. Anthracycline-based chemotherapy is an option for advanced disease; however, effective treatment of advanced soft tissue remains a challenge. Various combinations and dosages of conventional chemotherapeutic agents have not achieved significant improvements in overall survival.

Advances in understanding the genetic nature of cancer have led to the development of new treatment

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Abbreviations used in this paper: GIST = gastrointestinal stromal tumor, VEGFR = vascular endothelial growth factor receptor, PDGFR = platelet-derived growth factor receptor, TKI = tyrosine kinase inhibitor, DFSP = dermatofibrosarcoma protuberans, EGFR = epidermal growth factor receptor.

options for sarcoma. For example, gastrointestinal stromal tumors (GISTs) that harbor activating mutations in the *c-kit* gene are sensitive to treatment with imatinib mesylate, a tyrosine kinase inhibitor (TKI), whereas those without *c-kit* mutations are less sensitive. Evidence presented at the 2004 meeting of the American Society of Clinical Oncology (ASCO) demonstrated that patients with liposarcoma, leiomyosarcoma, and fibrosarcoma had objective response rates to imatinib despite absence of a *c-kit* mutation.⁸ Patients with advanced GIST who have progressed on imatinib treatment have a partial response rate of 8% and a stable disease rate of 70% when treated with sunitinib malate. This is a broad-spectrum, orally available, multitargeted TKI of vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR), c-Kit, and FLT-3 kinase.⁹ Sunitinib was approved by the US Food and Drug Administration for imatinib-refractory or intolerant GIST in January 2006. A plethora of novel drugs are in various stages of clinical development for GISTs. The example of GIST is encouraging and might become a model for developing new agents for the other sarcoma subtypes.

Aberrant Activation of TKs in Sarcomas

Genetically, sarcomas fall into two subgroups: those with complex karyotypes characteristic of severe ge-

netic instability and those characterized by near-diploid karyotypes. The sarcomas with simple, near-diploid karyotypes usually possess specific chromosomal translocations (Table 1). Sarcomas with complex karyotypes have high frequencies of p53 and RB mutations as well as impairments in DNA repair and demonstrate severe chromosomal instability. This group includes some of the more commonly diagnosed sarcomas such as leiomyosarcoma, rhabdomyosarcoma, and osteosarcoma. Many sarcomas that fall into both genetic subgroups also possess abnormalities in growth factor signaling and signal transduction pathways.

TKs make up the majority of defective signaling pathways in sarcomas, including mutations in the PDGFR, c-Kit, VEGFR, and insulin-like growth factor-1 receptor (IGF1-R) signaling pathways.¹⁰ For example, GISTs, Ewing's sarcoma, dermatofibrosarcoma protuberans (DFSP), synovial sarcoma, and Kaposi's sarcoma have all been shown to have mutations that elicit c-Kit protein overexpression and/or PDGFR overstimulation.

TKIs are a class of novel therapeutics that are effective alone and in combination with conventional chemotherapeutics in treating a variety of cancer subtypes. The two basic classes of TKs are receptor TKs and nonreceptor TKs. Upon TK activation, a cascade of protein interactions occurs and releases signals of positive and negative regulators of a variety of cellular processes including cell cycle regulation, proliferation, adhesion, migration, invasion, transcription, and survival. Under normal conditions, cellular signaling tightly regulates activated TKs. The induction of TK signaling in the oncogenic state overcomes controlled regulation, and signaling becomes activated by a myriad of cellular mechanisms including mutation and overexpression of the TK receptors or receptor ligands. All TKs rely on

Table 1. — Translocations Associated With Sarcomas

Translocation	Gene	Type of Fusion Gene
Ewing's sarcoma		
t(11;22) (q24;q12)	EWSR1-FLI1	Transcription factors
t(21;22) (q22;q12)	EWSR1-ERG	
t(7;22) (p22;q12)	EWSR1-ETV1	
t(17;22) (q21;q12)	EWSR1-ETV4	
t(2;22) (q33;q12)	EWSR1-FEV	
Clear cell sarcoma		
t(12;22) (q13;q12)	EWSR1-ATF1	Transcription factor
Desmoplastic small round cell tumor of the abdomen		
t(11;22) (p13;q12)	EWSR-WT1	Transcription factor
Myxoid liposarcoma		
t(12;16) (q13;p11)	FUS-DDIT3	Transcription factors
t(12;22) (q13;q12)	EWSR1-DDIT3	
Alveolar rhabdomyosarcoma		
t(2;13) (q35;q14)	PAX3-FOXO1A	Transcription factors
t(1;13) (p36;q14)	PAX7-FOXO1A	
Synovial sarcoma		
t(X;18) (p11;q11)	SYT-SSX	Transcription factor
DFSP		
t(17;22) (q22;q13)	COL1A1-PDGFB	Growth factor
Congenital fibrosarcoma		
t(12;15) (p13;q25)	ETV6-NTRK3	Transcription factor receptor
Alveolar soft-part sarcoma		
t(X;17) (p11.2;q25)	ASPL-TFE3	Transcription factor
Myxoid chondrosarcoma		
t(9;22) (q22-31;q11-12)	EWSR1-NR4A3	Transcription factor

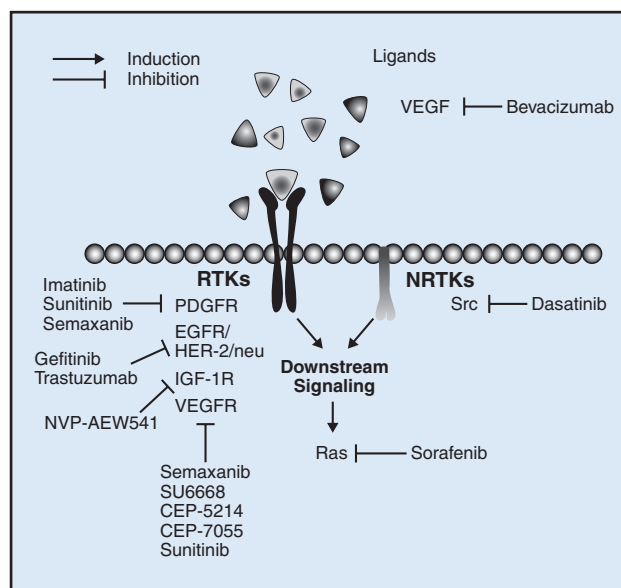


Figure. — Illustration of targeted TKIs as potential sarcoma therapy. RTK = receptor tyrosine kinase, NRTK = nonreceptor tyrosine kinase.

adenosine triphosphate (ATP) to mediate the transfer of energy in the kinase domain to elicit downstream signaling cascades via pathway intermediates. TKIs employ two strategies: (1) antibodies that act as receptor antagonists or to sequester the TK ligand, preventing the ligand from binding to the receptor TK, and (2) small molecule inhibitors that act by competing for the ATP-binding domain in the catalytic site of the enzyme (Figure). A review of the molecular biology of TKs and TKIs can be found elsewhere.¹¹

The use of TKIs for the treatment of sarcomas is predicated on the hypothesis that malignant cells rely more heavily than neighboring normal cells on TK signaling. This article reviews studies completed in both sarcoma research models and early phase trials to summarize the current state of TKIs in the treatment of non-GIST sarcomas (Table 2).¹²⁻⁴⁸

Applications of TKIs in Sarcomas

c-Kit

Advances in our understanding of the molecular abnormalities involving *c-kit* in GISTs have led to the development of highly effective novel therapies that inhibit kinase activity and consequently reduce tumor burden and improve survival. The transmembrane receptor tyrosine kinase c-Kit is defined by the CD117 antigen

and is the product of the *c-kit* proto-oncogene. Activating or gain of function mutations in the *c-kit* gene results in constitutive c-Kit tyrosine kinase activity.

The role of *c-kit* in the pathogenesis in other sarcomas has been investigated. The data regarding *c-kit* mutations and activity in Ewing's sarcoma are controversial. Scotlandi et al²⁶ demonstrated that c-Kit was expressed in 30% (n = 101) of primary Ewing's sarcomas evaluated, but no significant association between the expression of this kinase and the clinical outcome was observed. The effects of imatinib were evaluated on a panel of eight different Ewing's sarcoma cell lines. Imatinib inhibited proliferation by 50% and induced apoptosis at IC₅₀s ranging from 10 to 12 μM. An additive effect on growth inhibition was seen when 10 μM of imatinib was combined with increasing doses of doxorubicin. A decrease of stem cell factor-mediated Ewing's sarcoma cell migration was also found, suggesting an alternative growth inhibitory pathway other than the c-Kit/stem-cell factor axis.

In xenograft models, imatinib treatment resulted in regression and/or stabilization of primary Ewing's tumors.²⁷ Phase I clinical trials have demonstrated that the maximally tolerated dose of imatinib is 1,000 mg day,^{12,28,29} which corresponds to a physiologic concentration of 6 to 10 μM.³⁰ This concentration is below the

Table 2. — Development Stage of TKI-Targeted Agents in Sarcomas

Agent	Company	Targets	Stage of Development	References
Small Molecular Inhibitors				
Imatinib (Gleevec)	Novartis	c-Kit, PDGFR	Phase III GIST Phase II DFSP, Kaposi's sarcoma Preclinical osteosarcoma, malignant fibrous histiocytoma, Ewing's sarcoma	12-24 13, 25 12, 26-36
Gefitinib (Iressa)	AstraZeneca	EGFR family	Phase I Ewing's sarcoma Preclinical osteosarcoma, rhabdomyosarcoma	12, 26-36 37
Semaxanib	Pfizer	VEGFR, PDGFR	Phase II soft tissue sarcoma Preclinical neurogenic sarcomas, Ewing's sarcoma	38 39, 40
SU6668	Sugen	VEGFR	Preclinical Ewing's sarcoma	40
CEP-5213	Cephalon	VEGFR	Preclinical angiosarcoma	40, 41
CEP-7055	Cephalon	VEGFR	Preclinical angiosarcoma	41
NVP-AEW541	Novartis	IGF1-R	Preclinical osteosarcoma, Ewing's sarcoma, rhabdomyosarcoma	42
Dasatinib (Sprycel)	Bristol-Myers Squibb	Src	Phase II solid tumors	43
Sorafenib (Nexavar)	Bayer	Ras	Phase II Kaposi's sarcoma	44
Sunitinib (Sutent)	Pfizer	Pan TKI, PDGFR, VEGFR	Phase III refractory GIST	13, 44
Antibody-Targeted				
Herceptin (Trastuzumab)	Genentech	HER-2/neu	Preclinical Ewing's sarcoma	45, 46
Bevacizumab (Avastin)	Genentech	VEGF	Phase II osteosarcoma, soft tissue sarcoma, Ewing's sarcoma, Kaposi's sarcoma, alveolar soft part sarcoma Preclinical Ewing's sarcoma	44, 47, 48 40

IC₅₀ required to inhibit the proliferation and induce apoptosis of Ewing's sarcoma cell lines.³¹ Therefore, the preclinical data suggest that c-Kit is not a critical target for Ewing's sarcoma survival and thus may not serve a single-agent treatment option.

AIDS-related Kaposi's sarcoma is associated with HIV and Kaposi's sarcoma herpes virus/human herpes virus-8 co-infections usually found on the skin.²⁵ Kaposi's sarcoma has been shown to express high levels of both c-Kit and PDGFR, and imatinib has been evaluated as a potential therapeutic option for this sarcoma. A study consisting of 10 men with AIDS-related Kaposi's sarcoma received 300 mg of imatinib twice daily for 4 weeks. Of the 10 patients, 5 had partial clinical responses. The remaining 5 participants had stable disease at the end of the study, 2 of whom demonstrated histologic disease regression. This study demonstrated that imatinib has potential effectiveness as a treatment option for patients with AIDS-related Kaposi's sarcoma.²⁵

PDGF

PDGFs and their TK receptors (PDGFRs) have been implicated in pathogenesis of a number of sarcomas. Tumor growth can be promoted by PDGF via autocrine stimulation of malignant cells, overexpression or overactivation of its receptors, and/or stimulation of angiogenesis within the tumor.

Imatinib is a potent inhibitor of not only c-Kit/ABL but also PDGFR. Studies using imatinib have been completed in rat osteosarcoma and malignant fibrous histiocytoma (MFH) cell lines expressing high levels of PDGFR α . Imatinib inhibited 20% and 40% of cellular proliferation, respectively, when osteosarcoma and MFH cell lines were treated with 10 μ M of imatinib.³² Osteosarcomas have been shown to express high levels of PDGFR. However, preclinical studies have not shown that imatinib can achieve antitumor activity within clinically relevant or achievable doses.^{33,34}

DFSP is a slow-growing sarcoma that is locally invasive. When resected, it has a likelihood of recurrence. Most DFSPs have a characteristic translocation, t(17;22), that places the regulation of PDGF β , a ligand for PDGFR, in the control of the collagen 1A1 promoter. This induces overexpression of PDGF β . In vivo experiments conducted on nude mice carrying tumors induced by DFSP-transformed cells treated with imatinib demonstrated significant inhibition of tumor growth.³⁵

Clinical response to imatinib was assessed in a case series that included 8 patients with locally advanced DFSP with the characteristic t(17;22) translocation and 2 patients with metastatic disease.¹⁵ Patients were treated with 400 mg of imatinib two times daily. All 8 patients with local disease experienced a clinical response, 4 of whom had a complete clinical response of an average duration of 220 days. The patients with metastatic disease had more com-

plex karyotypes than those of the localized DFSPs. One patient with metastatic disease and the t(17;22) translocation achieved a partial response (198 of 383 days of follow-up) but experienced disease progression 7 months following treatment. The other patient with metastatic disease did not have the t(17;22) translocation and did not experience a clinical response. This study concluded that imatinib may be useful for treating localized and metastatic DFSP with the t(17;22) translocation. Imatinib has become a viable option for the treatment of DFSP.

An ongoing multi-institutional study by the Sarcoma Alliance for Research Through Collaboration (SARC) consortium is evaluating the activity of imatinib in non-GIST sarcoma subtypes based on the postulated mechanism of action involving inhibition of polymorphisms of PDGFR and/or downstream effectors. Early results demonstrate a progression-free survival benefit in liposarcoma, leiomyosarcoma, and fibrosarcoma; however, the final results have not been published.⁸ The Children's Oncology Group has recently published results of a phase II study of imatinib in refractory solid tumors that demonstrated no benefit in pediatric sarcoma.⁴⁹

EGFR

Epidermal growth factor receptor (EGFR) is a transmembrane glycoprotein that is overexpressed in a variety of human malignancies and is often associated with chemoresistance and a poor clinical outcome. Sato et al⁵⁰ demonstrated that 168 (60%) of 281 adult soft tissue sarcoma patient samples analyzed overexpressed EGFR. The most common subtypes are malignant fibrous histiocytoma (89%), myxofibrosarcoma (89%), synovial sarcoma (76%), malignant peripheral nerve sheath tumor (89%), and leiomyosarcoma (73%). Increased levels of EGFR were significantly correlated with poorer survival and higher histologic grade.

Gefitinib, an EGFR inhibitor, has shown potential antitumor effects in several sarcoma cell lines when used in combination with irinotecan, a topoisomerase I inhibitor.³⁷ Murine xenograft models have been used to assess the effects of gefitinib on implanted tumors. Gefitinib was administered using oral gavage at 100 mg/kg either once or twice daily for 5 days per week. The antitumor activity of the combination was greater than additive in one of the seven cell line-derived xenografts and enhanced the activity of irinotecan in three of the seven xenografts.³⁷

A phase I trial of gefitinib was completed on 25 children with refractory solid tumors. Twelve of the 25 patients enrolled were sarcoma patients. Gefitinib was administered once daily for a course of 28 consecutive days starting at 150 mg/m² and escalated to 500 mg/m². A median of 54 courses were delivered. After one course of treatment, a patient with recurrent Ewing's sarcoma experienced a partial response that lasted 10

weeks. The maximum tolerated dose in this study was 400 mg/m² per day and was well tolerated.⁵¹

While these early data appeared promising, phase II studies completed by the European Organization for Research and Treatment of Cancer (EORTC) and the Southwest Oncology Group (SWOG) with erlotinib in synovial sarcoma and with gefitinib in malignant peripheral nerve sheath tumors, respectively, demonstrated no clinical activity.

HER-2/neu

The human epidermal growth factor receptor-2 (HER-2) is a proto-oncogene located at chromosome 17q21 and encodes a 185-kDa transmembrane TK glycoprotein. Expression of HER-2 at diagnosis has been evaluated in musculoskeletal tumors: Ewing's sarcoma, osteosarcoma, and synovial sarcoma. Since there is conflicting evidence in the literature evaluating HER-2/neu as an effective target in treating sarcoma, the potential role of HER-2/neu as a therapeutic target for sarcoma is controversial.

HER-2 has been evaluated in Ewing's sarcoma by immunohistochemistry (IHC) in both clinical samples and cell lines. One group evaluated 5 Ewing's sarcoma cell lines and 13 archived primary Ewing's sarcoma samples for HER-2/neu gene amplification and protein expression. While several of the Ewing's sarcoma cell lines and tumor samples had high HER-2/neu protein expression, none had HER-2/neu gene amplification. In addition, upon assessment of trastuzumab (Herceptin), an anti-HER-2/neu monoclonal antibody that inhibits HER-2/neu expression and blocks tumorigenesis induced by HER-2/neu, the group determined that trastuzumab had minimal inhibitory effects on cell growth, survival, or colony formation of the Ewing's sarcoma cell lines evaluated.⁴⁵ Scotlandi et al⁵² evaluated the expression of HER-2 by IHC in 113 Ewing's sarcoma paraffin-embedded tumor biopsies. Overexpression of HER-2 was present in 16% of Ewing's sarcoma samples; however, there was no correlation found between prognosis and expression. No therapeutic value was observed in Ewing's sarcoma cell lines. Furthermore, others have evaluated trastuzumab alone and in combination with conventional chemotherapeutics used to treat sarcomas in two Ewing's sarcoma cell lines. These studies have not shown antitumor activity at clinically achievable doses.⁴⁶

HER-2/neu is not a major therapeutic target for the treatment of Ewing's sarcoma. These results argue that HER-2/neu is not a critical pathway for the pathogenesis of Ewing's sarcoma and that targeting this pathway alone might have little therapeutic benefit in Ewing's sarcoma patients.

Conflicting data have been reported for osteosarcoma. HER-2 protein expression by IHC at initial diagnosis has been correlated with both inferior clinical outcome and poor histologic response to chemotherapy. However, these findings have been challenged by oth-

ers. A study completed by Akatsuka et al⁵³ observed a positive association between amplified HER-2 expression and increased survival. Scotlandi et al⁵² evaluated 84 osteosarcoma paraffin-embedded tumor biopsies, of which 32% were shown to overexpress HER-2. HER-2 overexpression was significantly associated with increased expression of P-glycoprotein, which is responsible for multidrug resistance. Event-free survival evaluation demonstrated a prognostic value for both HER-2 and P-glycoprotein evaluation. However, there was no therapeutic value of single-agent trastuzumab observed in cell line studies. This correlates to findings by Hughes et al,⁵⁴ who demonstrated that cell surface co-expression of HER-2 and EGFR along with the nuclear localization of the activated p80 fragment of HER-4 contributes to the pathogenesis of osteosarcoma. Clinical trials are underway examining the efficacy of trastuzumab in osteosarcoma. The final results of these studies have not yet been reported.

Synovial sarcomas are high-grade soft tissue sarcomas characterized by biphasic spindle and epithelioid morphology. Most synovial sarcomas possess a translocation in which the proximal portion of chromosome 18q11 (SYT gene) is fused to the distal portion of several duplicated SSX genes (SSX1 and SSX2) at chromosome Xp11. SYT/SSX1 translocations are 3 times more common than SYT/SSX2 translocations and are associated with a more aggressive disease course.

Using IHC, Thomas et al⁵⁵ demonstrated that HER-2 expression in synovial sarcoma was restricted to tumors containing SYT/SSX2 translocations. Expression was minimal and no evidence of gene amplification was observed.

VEGFR

The growth, migration, and dissemination of sarcoma depend on angiogenesis. Generally, tumors cannot grow without developing a vascular supply. Neovascularization allows for growth of the primary tumor as well as a pathway for migrating tumor cells to gain access to the systemic circulation and establish distant metastases. Angiogenesis is regulated by a number of proangiogenic and antiangiogenic factors. VEGF is the most potent and specific of the endothelial cell mitogens. It acts as an endothelial cell survival factor as well as a key factor in mobilizing circulating endothelial cell precursors to nascent blood vessels. VEGF promotes the vascularization and growth of primary tumors and appears to play a role in establishing new metastatic foci. These processes make the inhibition of VEGF an attractive target for antiangiogenic therapy in cancer.

Semaxanib is a dual VEGFR and PDGFR inhibitor that has been evaluated in neurogenic sarcoma cell lines and human tumor explants. Semaxanib had no effect on cell lines *in vitro* at doses up to 200 μ M; however, it reduced proliferation in tumor explants by 54.8% in mice treated with 25 mg/kg/day for 8 days.³⁹

This growth reduction was due to decreased tumor angiogenesis, which led to decreased proliferation and increased apoptosis. While clinical development of semaxanib has been terminated, such in vitro data demonstrate a potential role of VEGF signaling in sarcoma growth and survival.

VEGFR inhibitors have been shown to be potent inhibitors of Ewing's sarcoma growth in mouse models. Several inhibitors of VEGF signaling have been evaluated in Ewing's sarcoma and have shown significant reduction of tumor growth in mouse models. The VEGFR inhibitors SU6668 at 25 mg/kg per day and semaxanib at 100 mg/kg per day, as well as the anti-VEGF agents bevacizumab (Avastin) at 10 mg/kg twice weekly and VEGF Trap at 2.5 or 25 mg/kg twice weekly significantly reduced tumor growth at clinically achievable doses.⁴⁰ Another VEGF-signaling inhibitor, CEP-5214, and its pro-drug CEP-7055 inhibit tumor growth in a mouse angiosarcoma model. CEP-5214 administration at 1 to 3 mg/kg per day for 10 days achieved the minimum effective dose, and the maximum efficacy was observed by treatment with 23.8 mg/kg CEP-7055 for 10 days. These preliminary data demonstrate the antitumor activity of these drugs and offer evidence to warrant further investigation into the possible therapeutic potential of these inhibitors for the treatment of angiosarcoma.⁴¹

In patients with soft tissue sarcoma, tumor VEGF expression correlates with stage, grade, and prognosis.⁴¹ In patients with osteosarcoma, elevated tumor and circulating VEGF levels are associated with the development of lung metastases. Other therapeutics that inhibit TK signaling through the use of antibodies such as angiogenesis inhibitors are currently undergoing clinical trials in sarcomas. Bevacizumab, a recombinant VEGF monoclonal antibody, has shown clinical promise by significantly increasing disease-free progression and overall survival in several malignancies including breast, renal cell, and colorectal cancers.⁴⁴ A phase II trial combining doxorubicin at 75 mg/m² with 15 mg/kg of bevacizumab given intravenously every 3 weeks was completed in patients with metastatic soft tissue sarcomas.⁴⁷ A 12% response rate was observed in this study, suggesting that bevacizumab in combination with doxorubicin had no greater response rate than doxorubicin as a single agent, although 65% of the patients experienced stable disease for 4 or more cycles. Several ongoing clinical trials are investigating the use of bevacizumab as a possible therapy for sarcoma.

IGFR

Consistent evidence shows that insulin-like growth factor receptor (IGF-1R) plays a significant role in human cancer. IGF-1R is a cell membrane receptor that is activated by IGF-1 and 2. It has demonstrated activity on cellular proliferation, differentiation, and prevention of apoptosis.

Activation by binding ligand leads to mitogenic and anti-apoptotic effects or to induction of differentiation with growth arrest, differentiation, or cell death.

IGF-1R is a target of great interest for the treatment of sarcomas. Ahlen et al⁵⁶ evaluated 101 patients with primary high-grade soft tissue sarcoma for IGF-1R expression. A significant association was shown to exist between elevated expression of IGF-1R and favorable prognostic outcome. Patients with high IGF-1R expression had a superior outcome compared with patients with a lower expression.

The therapeutic potential of NVP-AEW541, an IGF-1R inhibitor, was evaluated in a panel of 8 osteosarcoma, 10 Ewing's sarcoma, and 5 rhabdomyosarcoma cell lines. NVP-AEW541 induced cell cycle arrest in a dose-dependent manner in all of the cell lines tested when treated with 300 nM, 1 μM and 3 μM for 24 hours. Apoptosis was induced in all of the Ewing's sarcoma cell lines and in many of the osteosarcoma and rhabdomyosarcoma cell lines, which correlated with IGF-1R inhibition. These preliminary data provide promising evidence to further evaluate NVP-AEW541 as a potential therapeutic for the treatment of sarcomas.⁴² Currently, trials in early-stage development are evaluating IGF-R inhibitors in both bone and soft tissue sarcoma.

Pan-TKIs

Agents that inhibit multiple TKs are currently in clinical investigation for both bone and soft tissue sarcomas. These include dasatinib, sunitinib, and sorafenib.

Dasatinib, a small-molecule inhibitor of Src kinase activity, is a promising cancer therapeutic agent with oral bioavailability. Currently, dasatinib is approved for use in imatinib-refractory chronic myelogenous leukemia. The therapeutic potential of dasatinib was evaluated in 12 soft tissue and bone sarcoma cell lines. Dasatinib inhibited Src kinase activity at nanomolar concentrations (3 to 68 nM) all 11 of the cell lines that exhibited activated Src kinase activity. Inhibition of Src signaling was accompanied by blockade of cell migration and invasion, consistent with Src inhibition. Moreover, apoptosis was induced in the osteosarcoma and Ewing's subset of bone sarcomas at nanomolar concentrations of dasatinib, indicating that these bone sarcoma cell lines are dependent on Src activity for survival. These results demonstrate that dasatinib inhibits migration and invasion of diverse sarcoma cell types and selectively blocks the survival of bone sarcoma cells. Therefore, dasatinib might provide therapeutic benefit by preventing the growth and metastasis of sarcomas in patients.⁴³

Sunitinib is a pan-TKI that elicits inhibitory effects on a variety of TKs including PDGFRα, PDGFRβ, and VEGFR1–3. It has recently been approved for patients with refractory GIST⁴⁴ and is in various stages of clinical development as both single and combined modality therapy.

Sorafenib (Nexavar) is a multikinase inhibitor with effects on tumor proliferation and angiogenesis. Inhibitory activity has been demonstrated for the TKs for VEGF, PDGF, FLT-3, and c-Kit.⁵⁷⁻⁶¹ It has been approved for use in metastatic renal cell cancer and is in various stages of development in sarcoma. At the 2007 meeting of ASCO, preliminary results of a phase II study of sorafenib in advanced soft tissue sarcomas demonstrate some activity in angiosarcoma as well as disease control in other subtypes.⁶²

Conclusions

Effective treatment options for metastatic soft tissue sarcoma have yet to be demonstrated. As our experience with GIST has proven, dramatic improvements in patient outcomes can be made by targeting defined molecular alterations. More than 40% of sarcoma subtypes have known chromosomal translocations or amplifications; however, the function of which for the most part are widely unknown. We have an opportunity to alter the therapeutic options in patients with sarcoma as our understanding of the molecular events that underlie sarcoma development continues to expand. With the exponential development of small-molecule TKIs as well as the ongoing research into the gene products of the known chromosomal abnormalities in sarcoma, we might be able to improve the current care for this patient population.

Disclosures

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