Targeted Therapies for Sarcomas: The Next Generation of Treatments

An ESUN Article

David M. Loeb, MD, PhD
Assistant Professor, Oncology and Pediatrics
Director, Musculoskeletal Tumor Program
Sidney Kimmel Comprehensive Cancer Center
Johns Hopkins University
Baltimore, MD 21231

Limitations of Chemotherapy

The recognition that some sarcomas are sensitive to chemotherapy has led to remarkable improvements in outcome for patients with these diseases. Before chemotherapy, surgery alone cured less than 20% of patients with Ewing's sarcoma or osteosarcoma, even when they had localized disease. In contrast, patients with nonmetastatic Ewing's sarcoma now have a 5-year disease-free survival (DFS) rate of 60-70%, depending on treatment regimen (Grier et al., 2003). Similarly, the 5-year DFS for patients with nonmetastatic osteosarcoma treated with modern multi-agent chemotherapy is also in excess of 60% (Ferrari et al., 2005). Ongoing attempts to intensify chemotherapy have not resulted in further substantial improvements in survival rates. For example, 5-year DFS for patients with localized Ewing sarcoma treated on the IESS-II protocol with vincristine, actinomycin D, doxorubicin, and cyclophosphamide was 73% (Burgert et al., 1990), which is not dissimilar to the results of the most recent Children's Oncology Group (COG) trial, which were published 13 years later (Grier et al., 2003). The same observation applies to osteosarcoma as well: 4-year metastasis-free survival of patients with localized osteosarcoma with a good histological response to pre-surgery chemotherapy treated on the control arm of the COSS-82 study (published in 1988) was 77% (Winkler et al., 1988), which is superior to the 62% event-free survival reported for the SFOP-OS94 study published almost 20 years later in 2007 (Le Deley et al., 2007). The situation for patients with metastatic disease is similar. Although patients with metastatic Ewing sarcoma benefit from treatment with chemotherapy (survival for such patients on the most recently published COG protocol was greater than 20%) (Grier et al., 2003), as do patients with metastatic osteosarcoma (with 5-year overall survival in the same range (Seibel et al., 2007)), these survival rates are not significantly different from those reported more than 20 years ago. Thus, while chemotherapy clearly plays a role in the treatment of some sarcoma patients (having changed the survival rate from approximately 20% to approximately 70% for patients with localized osteosarcoma and Ewing sarcoma), subsequent refinements, including many attempts to intensify treatment, have not substantially improved upon these results. Because of that, new approaches to therapy are required.

The lack of improvement in outcomes despite treatment intensification argues against the likelihood that future manipulations of traditional chemotherapy will substantially improve the survival of sarcoma patients. Further, not all sarcomas are chemosensitive, and for patients with sarcomas that do not respond to chemotherapy, the role of adjuvant treatment remains controversial, as the minimal potential benefit may not justify the side effects. This is what underlies the drive to develop targeted therapies. There are many types of targeted therapies, but all share the same characteristic of attempting to capitalize on a biologic characteristic of the cancer cell to eradicate the tumor. The idea is that if a therapy targets some aspect of the cancer cell that is biologically necessary, it will be unlikely that the tumor will be able to develop resistance, thus making this type of treatment potentially more effective than traditional chemotherapy without as many side effects.

What is Targeted Therapy?

Targeted therapy is a treatment that aims to exploit some biologic feature of the tumor to eradicate it. This is in contrast to traditional chemotherapy, which is not specific to a particular
tumor type and acts by killing rapidly dividing cells, regardless of whether or not they are malignant. There are two major reasons for the development of targeted therapies: 1) by targeting a unique characteristic of the tumor, cancer cells will be killed while normal cells will be spared, thus providing effective cancer treatment with fewer side effects [both short term and long term (Oeffinger et al., 2006)], and 2) if the target is essential for the viability of the cancer, it is unlikely that the cancer cell will easily become resistant to the targeted therapy, thus increasing the effectiveness of this type of treatment.

Tumor angiogenesis is the growth of blood vessels between a tumor and its surrounding tissue. New blood vessels help the tumor to grow by feeding the cancer cells with essential nutrients and oxygen. Anti-angiogenesis agents or "inhibitors" are substances which prevent or destabilize the angiogenic process in a number of different ways (e.g., inhibition of endothelial cell growth and migration, suppression of the synthesis and degradation of the vessel basement membrane and extracellular matrix and blockage of angiogenic factors). There are many anti-angiogenesis agents in development and a number of agents currently being evaluated in clinical trials. Many have unique ways in which they perform their anti-angiogenic function.

Angiostatin is a piece (a fragment) of a protein, plasminogen, which plays a role in blood clotting. Angiostatin is normally secreted by tumors (at least in laboratory mice) and appears to halt the process of developing new blood vessels which is necessary to tumor development. It is hoped that Angiostatin may be used to develop a new class of anti-angiogenesis agents.

Endostatin is a piece (a fragment) of a protein, collagen 18, which appears in all blood vessels. Endostatin is normally secreted by tumors (at least in laboratory mice) and appears to halt the process of developing new blood vessels which is necessary to tumor development. It is hoped that Endostatin may be used to develop a new class of anti-angiogenesis agents.

Vascular Endothelial Growth Factor (VEGF) is a protein involved in the process that stimulates angiogenesis by binding to specific receptors on nearby blood vessels to grow extensions to existing blood vessels. An increased amount of VEGF in the bloodstream has been correlated with a poor prognosis in some tumor types. To date there are no surrogate markers for evaluating angiogenesis inhibitor efficacy. A monoclonal antibody, called rhuMab VEGF, has been developed that is designed to bind to VEGF and thus preventing the VEGF from binding to the receptors on the nearby blood vessels. It is hoped that this will prevent tumor growth. Bevacizumab (a.k.a. Avastin) is also a VEGF-based inhibitor.

Thrombospondin is one of a family of glycoproteins that are made in cells, secreted by cells, and incorporated into cells including blood platelets. The thrombospondins are known to interact with blood coagulation and anticoagulant factors. They are involved in cell adhesion, platelet aggregation (clumping), cell proliferation (growth), angiogenesis (blood vessel formation), tumor metastasis, and tissue repair. Thrombospondin-1 and thrombospondin-2 have been shown to be potent inhibitors of angiogenesis and suppressors of tumor growth in laboratory mice.

Matrix metalloproteinases is a member of a group of enzymes that can break down proteins that are normally found in the spaces between cells in tissues. These enzymes need zinc or calcium to work properly. Matrix metalloproteinases are involved in wound healing, angiogenesis, and tumor cell metastasis. Several matrix metalloproteinase inhibitors are being studied; among them is BMS-275291.

Chromosomal Translocations in Sarcomas: Genetic changes underlie the development of all human cancer. Such genetic changes can consist of point mutations in key genes (resulting in either nonfunctional genes or genes with altered function), small chromosomal deletions (eliminating the normal copy of a critical gene), or chromosomal translocations (which fuse parts of two genes, creating a novel, tumor-specific gene). A full discussion of genetic mutations, and of the role of epigenetic changes in the development of cancer, is beyond the scope of this article.

A number of sarcomas are characterized by the presence of specific chromosomal translocations (Table 1, below). Because each translocation results in the production of a novel, tumor-specific protein, these are tempting targets for the development of specific therapies. One successful application of this approach, discussed in depth in the text, is imatinib. This approach has met with limited success when applied to sarcomas.
There are several possible explanations for this lack of success. One explanation is that, although
the Philadelphia translocation that characterizes chronic myelogenous leukemia (CML) results in a
novel enzymatic activity, sarcoma-associated translocations predominantly affect transcriptional
regulators, which are significantly more difficult to inhibit specifically. The products of these
chromosomal translocations also generate novel epitopes that could be targeted by the patient’s
immune system. During tumorigenesis, the development of immunologic tolerance probably
prevents the targeting of these epitopes. Significant ongoing effort is being expended in
understanding how to break tolerance and allow the immunologic targeting of these epitopes, but
these efforts have not yet met with clinical success.

Table 1

<table>
<thead>
<tr>
<th>Tumor</th>
<th>Translocation</th>
<th>Fused Genes</th>
<th>Incidence (%)</th>
</tr>
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<tbody>
<tr>
<td>Ewing’s Sarcoma Family Tumors</td>
<td>t(11;22)(q24;q12)</td>
<td>EWS-Fli1</td>
<td>85</td>
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<td>Ewing’s Sarcoma Family Tumors</td>
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<td>EWS-ERG</td>
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<tr>
<td>Ewing’s Sarcoma Family Tumors</td>
<td>t(7;22)(p22;q12)</td>
<td>EWS-ETV1</td>
<td>Rare</td>
</tr>
<tr>
<td>Ewing’s Sarcoma Family Tumors</td>
<td>t(17;22)(q12;q12)</td>
<td>EWS-E1AF</td>
<td>Rare</td>
</tr>
<tr>
<td>Ewing’s Sarcoma Family Tumors</td>
<td>t(2;22)(q33;q12)</td>
<td>EWS-FEV</td>
<td>Rare</td>
</tr>
<tr>
<td>Desmoplastic Small Round Cell Tumor</td>
<td>t(11;22)(q13;q12)</td>
<td>EWS-WT1</td>
<td>95</td>
</tr>
<tr>
<td>Myxoid Liposarcoma</td>
<td>t(12;16)(q13;p11)</td>
<td>TLS-CHOP</td>
<td>95</td>
</tr>
<tr>
<td>Myxoid Liposarcoma</td>
<td>t(12;22)(q13;q12)</td>
<td>EWS-CHOP</td>
<td>5</td>
</tr>
<tr>
<td>Synovial Sarcoma</td>
<td>t(X;18)(p11.23;q11)</td>
<td>SYT-SSX1</td>
<td>65</td>
</tr>
<tr>
<td>Synovial Sarcoma</td>
<td>t(X;18)(p11.21;q11)</td>
<td>SYT-SSX2</td>
<td>35</td>
</tr>
<tr>
<td>Alveolar Rhabdomyosarcoma</td>
<td>t(2;13)(q35;q14)</td>
<td>PAX3-FKHR</td>
<td>75</td>
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<tr>
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<td>t(1;13)(p36;q14)</td>
<td>PAX7-FKHR</td>
<td>10</td>
</tr>
<tr>
<td>Congenital Fibrosarcoma</td>
<td>t(12;15)(p13;q25)</td>
<td>ETV6-NTRK3</td>
<td>Unknown</td>
</tr>
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</table>

**Different Types of Targeted Therapy**

**Molecularly targeted therapy**

Molecularly targeted therapy refers to a treatment designed to interfere with the function of a
biological pathway within the cancer cell that is critical to its growth or survival. Examples of
these pathways include signal transduction such as via the activation of kinases (enzymes that add
phosphates to target proteins, altering their function), programmed cell death (also called
apoptosis), regulation of gene transcription, or tumor angiogenesis (in growth of new blood
vessels). Molecularly targeted drugs are among the most commonly used targeted therapies to
treat sarcomas. The best known example of this type of treatment is a drug called imatinib. Originally developed as a specific inhibitor of the bcr/abl tyrosine kinase that characterizes chronic myeloid leukemia (CML), this drug was subsequently found to inhibit the activity of several other tyrosine kinases, including c-kit and the platelet-derived growth factor (PDGF) receptor. Tyrosine kinases, enzymes found in every cell, act by adding a phosphate group to a substrate protein. The phosphate group modifies the activity of the protein to which it is added, often activating it.

![Mechanism of action of imatinib](image.png)

Imatinib inhibits these kinases by binding to the active site on the kinase molecule. When imatinib is bound to the kinase, it cannot transfer the phosphate to the target protein, effectively shutting down the kinase. Some kinases are required for the continued survival of cancer cells, and inhibition of these kinases results in the death of the cancer cells. This is the basis of the efficacy of imatinib for the treatment of CML. Imatinib is a remarkably effective drug for the treatment of CML, resulting in a complete hematologic response in 95% of patients (Kantarjian et al., 2002).

Soon after the discovery that imatinib inhibits the bcr/abl tyrosine kinase and is an effective treatment for CML, it became clear that this drug is not as specific as first thought, and that it also inhibits the activity of other tyrosine kinases, including c-kit. The c-kit tyrosine kinase is important in the development of gastrointestinal stromal tumors, or GISTs. Over 85% of GISTs express c-kit, and the majority of these tumors have a mutation in c-kit that results in its being active all the time. This constant activity of an enzyme that normally should be turned on and off in response to environmental signals is thought to drive the growth of the tumor. Numerous studies have been published documenting that imatinib alone causes an objective response in anywhere from 48-71% of GIST patients (D’Amato et al., 2005). Thus, like CML, GIST can be treated effectively in many patients using this oral drug that targets the activity of an enzyme that is specifically critical for the growth of the tumor.

Based on these results, and on the observation that the PDGF receptor and c-kit are both found at high levels in a variety of pediatric sarcomas, the COG recently conducted a Phase II study of imatinib in recurrent or refractory solid tumors, including 24 patients with Ewing sarcoma, 10 patients with osteosarcoma, 10 with desmoplastic small round cell tumor, 1 patient with GIST, and 4 with synovial sarcoma. Of these 49 patients, 1 had a partial response and there were no complete responses (Bond et al., 2007), and COG concluded that imatinib has no role in the treatment of these tumors.

These disappointing results illustrate an important point regarding targeted therapy – just because a target is found in a tumor cell does not mean that inhibiting that target will be toxic to the cell. In some cases, for example bcr/abl in CML, the target is thought to initiate and propagate the cancer process. Inhibiting bcr/abl in CML cells is toxic to the cells, and the result is an effective cancer treatment. In contrast, the results of this COG trial suggest that activity of the PDGF receptor or c-kit is not required for the survival and propagation of the tumors; thus, inhibiting these enzymes had no clinical effect. The lesson to be learned is that molecularly targeted therapies must target processes that are essential to the viability of the tumor, or they will be ineffective.

Small molecules can be used not only to inhibit the function of cellular enzymes, but also to activate them. An important example of this phenomenon is the series of receptors for Tumor Necrosis Factor-related Apoptosis-inducing Ligand (TRAIL). TRAIL is a cytokine that binds to and activates two distinct cell surface receptors called Death Receptor 4 (DR4) and Death
Receptor 5 (DR5; Sheridan et al., 1997). Cytokines are small molecules that cells use to communicate with each other. When TRAIL binds to either DR4 or DR5, these receptors are activated and lead to the activation of pathways within the cell that ultimately lead to programmed cell death (apoptosis). There are so-called "decoy receptors" for TRAIL as well, and these "decoy receptors" bind TRAIL but do not activate cell death pathways (Sheridan et al., 1997). It is believed that the response of a cell to TRAIL depends, in large part, on the relative amounts of DR4, DR5, and the decoy receptors that are present on the surface of the cell. Interestingly, TRAIL only induces cell death in malignant cells, making this a promising system for molecularly targeted therapies (Pan et al., 1997). There is growing evidence that this cytokine/receptor system is particularly active in high grade sarcomas such as Ewing’s sarcoma (Mitsiades et al., 2001) and rhabdomyosarcoma (Petak et al., 2000), but this has not yet translated into a clinical trial.

Ligand targeted therapy

This refers to the use of antibodies that recognize proteins on the surface of tumor cells as a treatment modality. Examples of ligand targeted therapies include Herceptin for the treatment of breast cancer, Rituximab for the treatment of B cell lymphomas, and anti-GD2 for the treatment of neuroblastoma. Herceptin binds to the HER2/neu receptor on the surface of breast cancer cells (Simonds & Miles, 2007). This receptor is encoded by the ErbB2 gene, which is overexpressed (found at an inappropriately high level) in 25-30% of early stage breast cancers, and an even greater proportion of metastatic cases (Tsuda et al., 2001). Herceptin interferes with the function of the receptor, resulting in reduced tumor cell proliferation. Herceptin has been shown to be effective in treating HER2/neu-overexpressing breast tumors (Piccart-Gebhart et al., 2005) and was approved by the FDA in 1998.

Herceptin has also been investigated as a therapy for osteosarcoma. In 1999, Gorlick et al. reported overexpression of HER2/neu in 20 of 47 osteosarcoma samples, and showed that these patients had a poor response to therapy and a decreased rate of survival compared with patients whose tumors did not overexpress this antigen (Gorlick et al., 1999). Subsequent research has been divided about whether HER2/neu is commonly overexpressed, and whether or not overexpression has any impact on survival (Akatsuka et al., 2002; Thomas et al., 2002; Zhou et al., 2003). Nevertheless, a recently completed COG study incorporated Herceptin into the treatment of patients with metastatic osteosarcoma whose tumors overexpressed HER2/neu. Results of this study have not yet been released, but this is an example of incorporating ligand targeted therapy into the treatment of sarcoma patients.

Rituximab binds to a protein called CD20 that is found on the surface of mature B cells, including malignant lymphoma cells (Cvetkovic & Perry, 2006). When Rituximab binds to its target, it induces antibody-mediated cellular cytotoxicity (ADCC), complement-mediated cytotoxicity, and may even directly lead to cell death. ADCC refers to the process by which cytotoxic T lymphocytes are directed by antibodies to attack "foreign" cells. Thus, cells that are bound by Rituximab are targeted by two different arms of the patient’s immune system: the patient’s cytotoxic T lymphocytes are directed to kill lymphoma cells and the patient’s humoral immune system is activated as well. Ligand targeted therapies, therefore, can kill tumor cells in a variety of ways, including direct toxicity and helping the patient’s immune system to identify and eliminate these harmful cells.

Neuroblastoma, the most common solid tumor of childhood, is often characterized by expression of a cell surface marker known as GD2 (Schengrund & Shochat, 1988). A humanized monoclonal antibody against GD2 has been produced and incorporated into treatment of GD2-positive neuroblastomas. The mechanism of action of this antibody is not clear, but because GD2 is not thought to have a direct function in cell signaling, like HER2/neu does in breast cancer cells, ADCC and complement-mediated cytotoxicity are probably involved. No randomized studies of anti-GD2 antibodies have been performed, but one report from Memorial-Sloan Kettering Cancer Center suggests that their anti-GD2 antibody may improve the survival of patients with neuroblastoma involving bone marrow (Kushner et al., 2001). A COG study testing the effect of a different anti-GD2 antibody was recently completed, but the results have not yet been determined.

Passively targeted therapy
Passively targeted therapy refers to the modification of a drug to alter its delivery to its intended target, for example, liposomal formulations of chemotherapy drugs. A liposome is a vesicle with a lipid outer layer surrounding a water-filled center (Gabizon et al., 2006). There has been a major effort in the pharmaceutical industry over the past decade to develop liposomal formulations of various drugs, with the hopes of preferentially delivering drug to target lesions with less drug delivery to vital organs, hopefully resulting in fewer side effects. The predominant mechanism by which a drug encapsulated in a liposome targets a tumor is known as the EPR (for enhanced permeability and retention) effect – which is related to differences in blood vessel (capillary) integrity in tumors compared to normal tissues. Tumor capillaries are more "leaky" than capillaries in normal tissue, and tumors lack functional lymphatic drainage, so that particles which leak into the tumor tissue from the capillaries have no mechanism to be cleared away. These characteristics allow the accumulation of liposomes in the extracellular fluid of the tumor, where they slowly release the drug. This results in very high local concentrations, and relatively spares the normal organs (Maeda, 2001). In addition, by avoiding the cells that are usually responsible for clearing the drug from the circulation, drug exposure time is increased.

There are clinical trials published showing that liposomal doxorubicin is as effective as conventional doxorubicin, if not more effective, with less cardiotoxicity, in women with breast cancer. In one study, 296 patients with metastatic breast cancer were randomly assigned to treatment with either liposomal doxorubicin plus cyclophosphamide (142 patients) or conventional doxorubicin plus cyclophosphamide (155 patients). The response rate (complete plus partial responses) was 43% for both groups, but 21% of the patients who received conventional doxorubicin developed cardiotoxicity, compared with only 6% of the patients treated with the liposomal form (Batist et al., 2001). Moreover, there is evidence that tumors that clinically are resistant to standard doxorubicin can respond to liposomal doxorubicin. Batist et al. described 68 women treated with either conventional or liposomal doxorubicin, also in combination with cyclophosphamide, after having received prior chemotherapy with conventional doxorubicin (Batist et al., 2006). Thirty-one percent of the patients treated with liposomal doxorubicin responded to the chemotherapy, compared with only 11% of the patients retreated with conventional doxorubicin. Based on these and many other published studies, other liposomal drugs are being developed and tested, including different chemotherapy drugs (lurtotecan) and anti-angiogenesis drugs (drugs designed to interfere with blood vessel growth and integrity, rather than directly killing tumor cells) (Park et al., 2004). The latter are particularly exciting because, based on the proposed EPR mechanism of targeting, liposomal anti-angiogenesis drugs should be particularly effective anti-tumor agents.

Cardiomyopathy in Sarcoma Patients Why is the reduction in cardiotoxicity important? In a recent publication by the German Late Effects Surveillance System, 7.5% of patients treated for sarcomas on a variety of protocols run by the German Society of Pediatric Oncology and Hematology were diagnosed with doxorubicin-induced cardiomyopathy (Paulides et al., 2006). The mean cumulative doxorubicin dose was a modest 290 ± 91 mg/m². As total cumulative doses of doxorubicin increase, so will the rate of cardiomyopathy. Although the introduction of cardioprotection (in the form of dexrazoxane) is expected to ameliorate this toxicity, the development of less toxic alternatives to doxorubicin would be a significant benefit to sarcoma patients.

Physiologically targeted therapy

Physiologically targeted therapy refers to the use of radioactively-conjugated biochemical precursors that are concentrated in tumor cells based on some aspect of their unique physiology. Two emerging examples of this type of targeting include the use of 131I-metaiodobenzylguanidine (MIBG) for the treatment of neuroblastoma and the use of 153Sm-ethylenediaminetetramethylene phosphonic acid (EDTMP) for the treatment of osteosarcoma. Each of these treatments capitalizes on a unique aspect of tumor physiology to direct a cytotoxic radiopharmaceutical preferentially to the cancer, sparing most normal tissue.

Radioconjugated MIBG has been used as a diagnostic modality for patients with neuroblastoma for quite some time. Neuroblastoma is a tumor of sympathetic neuron precursor cells, and these cells normally synthesize epinephrine and related compounds, known as catecholamines. Because
neuroblastoma cells are derived from cells that synthesize catecholamines, 90% of tumors take up MIBG from the bloodstream, concentrating this drug in the tumor mass. Attaching 131I to MIBG allows the detection of neuroblastoma using a nuclear medicine scan. More recently, the New Approaches to Neuroblastoma Therapy (NANT) consortium has completed a phase I clinical trial evaluating whether cytotoxic doses of 131I-MIBG can be delivered to neuroblastoma lesions, and whether or not this will improve survival for patients with high risk disease (Matthay et al., 2006). In this study, patients who would otherwise be eligible for an autologous peripheral blood stem cell transplant were given a dose of 131I-MIBG 21 days prior to a standard chemotherapy-based transplant. Using standard nuclear medicine scanning, uptake of 131I-MIBG at sites of disease was confirmed. Six of 22 assessable patients had either a complete or a partial response (27%) and another 15 had either a mixed response or stable disease. The overall 3-year EFS was 31%, and overall survival at 3 years was 58%, excellent results for a phase I study. A confirmatory Phase II study is currently underway, but these results strongly suggest that targeted delivery of radiopharmaceuticals can be effective treatment for patients with high risk cancer.

A similar approach has been pursued for patients with high risk osteosarcoma using 153Sm-EDTMP. This compound consists of a radioisotope (153Sm) conjugated to a tetraphosphonate compound that localizes to sites of bone turnover, such as a metastatic bone lesion. Because 153Sm-EDTMP targets bone lesions by a mechanism similar to the radiotracer used in a bone scan, lesions that are visible on bone scan, including both primary osteosarcoma and metastatic deposits, are likely to be targeted by this agent. In addition to emitting radioactivity that can kill tumor cells, 153Sm emits a radioactive particle that can be detected by the same instrument used for a diagnostic bone scan, allowing uptake at a target tumor to be confirmed and the amount of radiation delivered to the tumor to be measured. The half-life of 153Sm is very short (46 hours) and the path length of the radiation (the distance the radioactivity travels within the body) is also very short, so that there are few side effects associated with its use. This compound was originally tested in adult patients with bone metastases from carcinomas, such as breast and prostate cancer, and has been approved for palliation of painful metastases by the FDA. In 2002, Anderson and colleagues published the results of a Phase I study of 153Sm-EDTMP for the treatment of high risk osteosarcoma patients (Anderson et al., 2002). In that study, 30 patients were treated with increasing doses of 153Sm-EDTMP from 1-30 mCi/kg. Because this compound significantly depresses bone marrow function, patients were rescued with an infusion of autologous peripheral blood stem cells 14 days after treatment. Other than low blood counts, the only side effect was transient low blood calcium seen only in patients treated with the highest dose. All of the patients began the trial requiring narcotics for pain relief, and every patient experienced a decrease or elimination of their narcotic requirement. In an attempt to improve efficacy, this group subsequently treated patients with gemcitabine, which is a chemotherapy drug that is thought to also act as a radiation sensitizer [a compound that makes a tumor more sensitive to radiation (Anderson et al., 2005)]. Fourteen patients were treated with high dose 153Sm-EDTMP followed one day later by gemcitabine. After 2 weeks, autologous peripheral blood stem cells were reinfused to ameliorate the expected low blood counts. At 6-8 weeks of follow-up, there were 6 partial remissions and 2 mixed responses, but none of these responses were durable. Thus, 153Sm-EDTMP shows promise for treating osteosarcoma, but further work will be required to determine its optimal use.

Selected Ongoing Clinical Trials Involving Targeted Therapy

The following discussion highlights select ongoing clinical trials of targeted therapies, with a focus on sarcomas. It is not intended to be comprehensive, nor should inclusion or exclusion of any particular trial be interpreted as endorsement of the trial or as a treatment recommendation.

Molecularly Targeted Therapies

**Dasatinib.** Although, as discussed above, imatinib has little activity against childhood sarcomas, other small molecule tyrosine kinase inhibitors might be more effective. One such drug that is now being tested in sarcoma patients is dasatinib. Originally developed for CML patients with imatinib resistant disease (Shah et al., 2004), this molecule also inhibits src kinase family members (O'Hare et al., 2006). Expression of src kinase family members, and other tyrosine kinases that might be inhibited by dasatinib, has been demonstrated in many types of sarcoma (Weiner et al., 1994). Thus, it is possible that, by virtue of having a wider range of targets, dasatinib might have activity where imatinib does not. The Children’s Oncology Group (COG) is currently running a
Phase I study of dasatinib for patients between the ages of 1-21 with recurrent or refractory extracranial solid tumors (as well as patients with imatinib-resistant CML or Philadelphia chromosome-positive ALL, acute leukemia that has the same chromosome translocation as CML). The Sarcoma Alliance for Research through Collaboration (SARC) has recently opened a Phase II study of dasatinib, specifically for sarcoma patients ages 13 years and older.

It is quite possible that inhibition of a single survival pathway with a small molecule such as dasatinib, will never be sufficient treatment for a sarcoma, but that small molecule kinase inhibitors might function best in combination with other therapies. To begin to test this concept, there are single institution trials of dasatinib with cetuximab (a monoclonal antibody that recognizes the epidermal growth factor receptor, EGFR) and dasatinib with gemcitabine. The University of Pittsburgh is conducting a Phase I trial of dasatinib in combination with cetuximab, with the ultimate goal of determining if the inhibition of these two critical signaling pathways (src and EGFR) will provide more effective treatment for advanced solid tumors than inhibition of either pathway alone. Similarly, MD Anderson Cancer Center is testing the combination of dasatinib with the chemotherapy agent gemcitabine to determine whether targeted therapies can improve the effectiveness of more traditional cytotoxic chemotherapy.

Sorafenib. While dasatinib targets tyrosine kinases that participate in the regulation of cellular survival and proliferation, sorafenib is less specific in its targeting, and therefore affects even more pathways, including angiogenesis (the growth of new blood vessels). Among the kinases inhibited by sorafenib are both major receptors for vascular endothelial growth factor (VEGF), the PDGF receptor, c-kit, ret, and raf, which is an intracellular serine/threonine kinase that functions downstream of the other kinases targeted by sorafenib (Wilhelm et al., 2006). This ubiquitous activity, while less elegant than a highly specific kinase inhibitor, may result in a more effective drug, as expression studies do not always predict which kinases are critical for cell function, and which can be lost (or inhibited) without effect on the cell. Sorafenib is now FDA approved for the treatment of renal cell carcinoma, and studies in other tumor types are ongoing. Among the trials relevant for sarcoma patients are a Phase II study of sorafenib for patients with soft tissue sarcoma led by the Dana-Farber Cancer Institute and a Phase I study combining sorafenib with bevacizumab (a VEGF receptor antibody) for patients with recurrent or refractory solid tumors being conducted at the National Cancer Institute.

Ongoing trials of tyrosine kinase inhibitors for the treatment of sarcomas, in light of the failure of the imatinib trial, might suggest that the lessons of that trial were not learned. However, the recognition that imatinib (though developed specifically as a bcr/abl inhibitor) and dasatinib (though developed specifically to inhibit the activity of mutant forms of bcr/abl that are resistant to imatinib) both inhibit a number of tyrosine kinases, suggests that our original view of these kinase inhibitors as specific to a single molecule was naive. It is likely that any efficacy seen in trials of these molecules will result, not from the inhibition of a single tyrosine kinase, but rather from inhibition of a group of kinases. Thus, successful treatment of sarcomas will likely result from the inhibition of the correct panel of kinases, and testing of less specific kinase inhibitors (optimistically renamed "multi-kinase inhibitors") is a sensible approach to targeted therapies for sarcomas.

Ligand Targeted Therapy

Anti-IGF1R. Insulin-like growth factor-1 (IGF-1) is a hormone that has been implicated in multiple processes related to the development of tumors, including resistance to apoptosis (programmed cell death) and the regulation of cell proliferation, angiogenesis (new blood vessel growth), and metastasis (Pollak, 2004). IGF-1 works by binding to a tyrosine kinase cell surface receptor. Binding to the receptor triggers receptor dimerization (the process by which two receptors bond together and become activated), which activates the intracellular kinase domain, generating a signal via the phosphorylation of multiple target proteins. IGF-1 and its receptor, IGF-1R, are members of a family of molecules that include insulin and its receptor, and IGF-2 and its receptor. Insulin receptor and the IGF-1R both activate intracellular signaling pathways, such as the MAP kinase pathway and the Akt pathway, which ultimately result in cell proliferation and resistance to apoptosis. IGF-1R is expressed in most tumor types, suggesting that a drug targeting this molecule might be effective against a wide range of cancers. Although activating mutations have not been identified to date, and gene amplification is quite rare, making firm implication in oncogenesis difficult, several lines of evidence implicate IGF-1R in the development of sarcomas.
Fibroblasts that were genetically engineered to lack IGF-1R were unable to be transformed by the EWS-Fli1 oncogene that defines Ewing sarcoma family tumors (Toretsky et al., 1997). Inhibition of IGF-1R function, either with a monoclonal antibody or with antisense oligonucleotides (small, synthetic DNA molecules that interfere with the production of the receptor itself) resulted in decreased growth and tumorigenesis of Ewing sarcoma cell lines (Toretsky et al., 1997). Phosphorylated, and presumably activated, IGF-1R has been detected in osteosarcoma, rhabdomyosarcoma, and Ewing sarcoma cell lines, and the growth of these lines was diminished by an inhibitor of the receptor’s tyrosine kinase activity (Scotlandi et al., 2005).

Because of these findings in sarcomas, as well as similar findings in other, more common, tumor types, there has been significant effort by the pharmaceutical industry to create agents that target this receptor. Humanized monoclonal antibodies against IGF-1R have been developed by at least 6 pharmaceutical companies, and agents developed by ImClone, Pfizer, Merck, and Amgen are in early phase clinical trials. Multi-center trials of these agents for patients with sarcomas are being planned by the pharmaceutical companies both alone and in collaboration with SARC (Sarcoma Alliance for Research through Collaboration).

Physiologically Targeted Therapies

**Samarium-153.** Contrary to common belief, osteosarcoma is sensitive to radiation, if administered at high enough doses. However, radiation is seldom used to treat osteosarcoma because of the high doses required to kill the tumor. For tumors of the extremities, surgery is superior for local control, and for tumors with pulmonary metastases, the tissue tolerance of surrounding normal lung is too low to allow the use of tumoricidal doses of radiation. However, targeted radiotherapy would be an attractive approach to the treatment of unresectable primary tumors, such as in vertebral bodies and the pelvis, as well as for patients with multiple bone metastases. One promising agent being developed for this purpose is 153Sm-ethylendediaminetetramethylene phosphonic acid (153Sm-EDTMP). As discussed above, because EDTMP is structurally related to the agent that is responsible for the localization of the imaging isotope in a bone scan, this allows delivery of the samarium-153 to lesions that are visible on bone scan. The radioactive properties of samarium-153, in addition to killing tumor cells, allow its distribution to be imaged using the same equipment that is used for a standard bone scan. Tumor uptake can therefore be quantified to ensure that adequate radiation was delivered.

The results of two prior clinical trials of this agent for the treatment of osteosarcoma have been published. The first of these was a Phase I study that showed that the dose limiting toxicity was suppression of bone marrow function, and that this could be bypassed by the administration of the patient’s previously harvested peripheral blood stem cells (Anderson et al., 2002). No other significant toxicities were reported. Although every patient on that study had a reduction in their pain, none achieved prolonged disease control. In an attempt to improve upon these results, a second clinical trial combined 153Sm-EDTMP with gemcitabine, which can act as a radiation sensitizer. Although objective responses were seen in these patients, none of the responses were durable (Anderson et al., 2005). Clearly, further work is required to determine the optimal use of this agent and its role in the treatment of osteosarcoma patients.

Two clinical trials of 153Sm-EDTMP for patients with osteosarcoma are currently open and accepting patients. Both are being run at Johns Hopkins. The first of these is a dose finding study, with a goal of identifying a dose of the agent that will allow reliable blood count recovery in 6 weeks without stem cell support. The second is a trial of two consecutive doses of 153Sm-EDTMP, one lower and one higher, with autologous peripheral blood stem cell support to see if this will be more effective than a single treatment.

**Radiolabeled octreotide.** Receptors for the neuroendocrine hormone somatostatin have been identified in a variety of sarcomas. In one study, 84% of soft tissue sarcomas expressed mRNA for somatostatin receptors, and 7 of 8 tumors were visible on an octreotide scan, a nuclear medicine study that visualizes tumor that expresses this receptor (Florio et al., 2003). Somatostatin receptors are also frequently found on osteosarcoma and Ewing sarcoma cells. This finding provides another opportunity for physiologically targeted radiotherapy, and this is being explored in a clinical trial being run by the University of Iowa. This dose escalation study aims to treat patients between the ages of 2 and 25 who are diagnosed with advanced or refractory solid tumors that are visualized on an octreotide scan. Patients will be treated with increasing doses of
90Y-labeled octreotide, with a goal of using the affinity of this agent for somatostatin receptors to deliver tumoricidal radiotherapy with minimal systemic toxicity.

**Conclusion**

The recognition that some sarcomas are sensitive to chemotherapy profoundly altered treatment outcomes, for example, increasing survival of patients with localized osteosarcoma from 20% to 70%. Unfortunately, the last 2 decades have seen a plateau in this progress, and chemotherapy has not altered the poor prognosis of patients with metastatic disease. Future progress is likely to arise, not from the discovery of new cytotoxic chemotherapeutics, but rather from the development of targeted therapies. There are multiple mechanisms by which therapies can be targeted, each of which is currently being developed for sarcoma patients. These new treatments hold substantial promise to improve outcomes for patients with sarcomas without significantly increasing toxicity. As our understanding of the biology of these tumors increases, a parallel expansion of effort toward the development of targeted therapies is highly anticipated.

**References**


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