Experimental Therapies and Clinical Trials in Bone Sarcoma

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Osteosarcoma, Ewing’s sarcoma, chondrosarcoma, bone sarcoma, clinical trial

Abstract
Sarcomas originating in the bone represent a challenge for physicians and patients. Because they constitute only 0.2% of all adult malignancies and 6% of pediatric malignancies, resources for studying this disease are often limited. Nonetheless, significant advancements have been made in the treatment of this disease, and there are ongoing efforts toward improvement. This article discusses recently completed and currently enrolling clinical trials for the 3 most common bone sarcomas: osteosarcoma, Ewing’s sarcoma family tumors, and chondrosarcoma. (JNCCN 2010;8:715–725)

Sarcomas originating in the bone represent a challenge for physicians and patients. Because they constitute only 0.2% of all adult malignancies and 6% of pediatric malignancies, resources for studying this disease are often limited. In the United States, more than 2500 patients are diagnosed annually with a primary bone cancer, and more than 1400 will die of the disease. Table 1 presents the major categories and relative frequency of bone cancers. The most common primary bone cancers are sarcomas, specifically osteosarcoma, chondrosarcoma, and Ewing’s sarcoma (EWS). Survival has improved for osteosarcoma and EWS, with cure rates increasing almost 4-fold (~ 15%–60%) over the past 30 years, as multidisciplinary management has integrated neoadjuvant and adjuvant chemotherapy with local disease control.

Although current first-line regimens for osteosarcoma and EWS have vastly improved patient outcomes, a paucity of effective treatment options remains for patients in the relapsed and refractory setting of both diseases. Chondrosarcoma remains a disease without any effective systemic therapy.

This article provides an overview of currently available experimental treatments and clinical trials in bone sarcomas, and the hypotheses behind them, for the most common bone sarcomas: osteosarcoma, EWS, and chondrosarcoma. A few recently completed studies are also discussed.

Osteosarcoma
More than 800 cases of osteosarcoma are diagnosed annually. The standard of care for patients with localized disease includes intensive neoadjuvant chemotherapy with a combination of the following agents: doxorubicin, cisplatin, and methotrexate. This standard was developed after a series of trials in the United States and Europe sequentially examined different chemotherapy regimens. These trials were instrumental in increasing the cure rate of patients with localized osteosarcoma from approximately 20% to between 60% and 76%.

Since the dramatic improvement in overall survival in the 1980s, relatively little advancement has occurred in the care of patients with osteosarcoma. Approximately 15% of patients diagnosed with high-grade osteosarcoma present with metastatic disease, and one third eventually develop it. After relapse, the median overall survival of patients with osteosarcoma remains approximately 11 months. Unfortunately, no effective salvage regimen exists for patients with relapsed osteosarcoma. A few therapies have shown marginal improvement in outcome, including ifosfamide/
and a trend toward improved 6-year event-free survival (61%–68%; \( P = .08 \)) were observed in patients treated with MTP-PE; no significant difference was seen in the chemotherapy arms. The arm with the best outcome included ifosfamide and MTP-PE, with a 6-year overall survival rate of 81%, suggesting that this combination may have particular benefit in osteosarcoma.\(^{23}\) MTP-PE remains an investigational agent in the United States, but was approved by the European Medicines Agency for postoperative treatment of localized osteosarcoma in combination with chemotherapy. Further study of its role in the treatment of this disease is warranted.

The European and American Osteosarcoma Study Group (EURAMOS) is currently conducting an international study of patients with localized or metastatic osteosarcoma initially treated with conventional MAP (NCT00134030). After surgery and assessment of histologic response, patients who experience a good histologic response are randomized to receive additional MAP with or without pegylated interferon \( \alpha \)2b (PEG-IFN\( \alpha \)2b). Patients who achieve a poor histologic response are randomized to maintenance MAP with or without ifosfamide and etoposide. The first question the study seeks to answer is whether the addition of ifosfamide and etoposide to maintenance MAP therapy improves the event-free survival of patients experiencing a poor histologic response to induction MAP.

The other important question that EURAMOS-1 hopes to answer is whether the addition of PEG-IFN\( \alpha \)2b can improve event-free survival in patients with a good histologic response to induction MAP. IFNs have been shown \( \textit{in vitro} \) to have a direct effect on tumor cells by inhibiting growth of tumor cells through unclear mechanisms and by affecting the differentiation of cells.\(^{24,25}\) Indirectly, IFN can regulate the immune system to activate macrophages and natural killer cells, and also has anti-angiogenic properties.\(^{26,27}\) \( \textit{In vitro} \) and \( \textit{in vivo} \) studies showed growth arrest in osteosarcoma cell lines and mouse models with IFN\( \alpha \).

Clinically, a series of 89 patients treated adjuvantly with IFN\( \alpha \) alone for high-grade osteosarcoma at the Karolinska Hospital from the 1970s to the 1990s suggested a role for IFN, particularly when given in higher doses for prolonged periods.\(^{28}\) The 10-year overall survival rate of 39% represented a vast improvement compared with historical controls.

<table>
<thead>
<tr>
<th>Classification of Most Common Bone Tumors</th>
<th>Relative Frequency</th>
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<tbody>
<tr>
<td>Osteosarcoma</td>
<td>35%</td>
</tr>
<tr>
<td>Chondrosarcoma</td>
<td>25%</td>
</tr>
<tr>
<td>Ewing’s sarcoma</td>
<td>16%</td>
</tr>
<tr>
<td>Chordoma</td>
<td>8%</td>
</tr>
<tr>
<td>Malignant fibrous histiocytoma of bone</td>
<td>5%</td>
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carboplatin/etoposide, gemcitabine/docetaxel, and high-dose ifosfamide.\(^{17–20}\) This article discusses recently completed and ongoing clinical trials using various strategies to improve the outcome of patients with osteosarcoma.

**First-Line Therapy Trials**

Multiple studies have examined different iterations of standard first-line cytotoxic therapy for osteosarcoma. One adaptation was OS99, a multi-institutional study of carboplatin, ifosfamide, and doxorubicin in 72 patients with localized osteosarcoma. A preliminary report showed 4-year overall and event-free survival rates of 68% and 82%, respectively. The outcomes were similar to those for treatments containing cisplatin and methotrexate, which are often difficult to tolerate or administer.\(^{21}\) These preliminary findings suggest that carboplatin, ifosfamide, and doxorubicin may be substituted for cisplatin or methotrexate when these drugs cannot be tolerated safely, with no negative effect on outcome.

Another recently completed study of first-line osteosarcoma therapy is U.S. Intergroup Study 0133, which studied the addition of ifosfamide or muramyl tripeptide phosphatidylethanolamine (MTP-PE) in 662 patients with localized disease.\(^{22}\) MTP-PE is an analog of muramyl dipeptide, a cell wall component of Bacille Calmette-Guérin, which has been encapsulated in liposomes and is believed to act as an immune-stimulator. In this study, patients with osteosarcoma underwent standard cisplatin, doxorubicin, and methotrexate (MAP) therapy initially. Patients were then randomized to receive or not receive ifosfamide and/or MTP-PE and MAP. Improved 6-year overall survival (70%–78%; \( P = .03 \))
treated without IFN or other systemic therapy. IFNβ was studied formally in Cooperative Osteosarcoma Study Group 80, a randomized study of localized osteosarcoma comparing 2 different chemotherapy regimens with or without adjuvant intravenous IFNβ for 22 weeks. This study did not show a significant difference in disease-free survival with or without IFN, but used a relatively lower dose of IFN for a shorter period. Overall, the preclinical and clinical data suggest that IFN may have some benefit as an adjuvant treatment in osteosarcoma; the current EURAMOS study is evaluating this hypothesis.

**Bisphosphonates**

Bisphosphonates are a class of drugs that inhibit bone resorption through suppressing osteoclast action. Through inducing apoptosis and inhibiting various enzymes, including farnesyl diphosphate synthase, bisphosphonates effectively block the mevalonate pathway, which is implicated in many cancers. Bisphosphonates reduce osteolytic bone metastases in many cancers, including breast cancer, myeloma, and prostate cancer. These effects may result from bisphosphonates’ effect on osteoclasts, angiogenesis, and potentially a direct tumor effect. In vitro data suggest that bisphosphonates can inhibit growth and proliferation in osteosarcoma cell lines. Preliminary results of a phase II study of pamidronate and standard chemotherapy in patients with newly diagnosed osteosarcoma showed that the combination was safe and well tolerated.

Several currently enrolling clinical trials are evaluating the use of bisphosphonates in osteosarcoma (Table 2). The Children’s Oncology Group is evaluating zoledronic acid in patients with newly diagnosed metastatic osteosarcoma in a single-arm trial (NCT00742924). This study has the goal of determining the safety and maximum tolerated dose of zoledronic acid when administered with standard cytotoxic agents in metastatic osteosarcoma. Secondary end points include histologic response and event-free survival, which will be compared with historical controls.

A randomized phase III study by the Federation Nationale des Centres de Lutte Contre le Cancer in France is evaluating standard chemotherapy with or without zoledronic acid in patients with previously untreated high-grade osteosarcoma, with progression-free survival as the primary end point (NCT00470223). Similarly, Tata Memorial Hospital in India is conducting a randomized study of 40 patients with osteosarcoma undergoing standard chemotherapy with or without zoledronic acid for 6 doses (NCT00691236). Another group of patients who are not candidates for standard chemotherapy will receive zoledronic acid as a single agent for 6 doses. Together these studies will help to establish the role of bisphosphonates in the treatment of osteosarcoma.

**Src Kinase Inhibition**

Multiple preclinical studies have suggested that inhibiting the Src family of tyrosine kinases may be beneficial in the treatment of osteosarcoma. Activated Src kinase can trigger many signaling pathways involved in cancer cell survival, proliferation, and motility, including PI3 kinase, Ras/Raf, and STAT3 pathways, and focal adhesion kinase and paxillin. CD99 and Caveolin-1 have also been implicated in reducing osteosarcoma metastases, presumably through inhibition of Src kinase.

Multiple clinical trials are currently evaluating the role of Src kinase inhibition in osteosarcoma (Table 2). The Sarcoma Alliance for Research through Collaboration (SARC) is conducting a double-blind randomized phase 2.5 study of AZD0530, an oral selective Src/Abl kinase inhibitor (NCT00752206). Patients with recurrent osteosarcoma metastatic to the lung who undergo metastasectomy are randomized to AZD0530 versus placebo for 1 year, with a primary end point of progression-free survival.

Dasatinib is also an oral inhibitor of the Src family of kinases (SRC, LCK, YES, FYN), in addition to BCR-ABL, ABL, KIT, EPHA2, and PDGFRβ. SARC recently completed enrollment to the osteosarcoma cohort of patients in a multicenter phase II study of dasatinib in advanced sarcomas. The final results are pending. A pediatric phase I/II study of dasatinib in combination with cytotoxic chemotherapy of ifosfamide, carboplatin, and etoposide is currently enrolling (NCT00788125). Eligible patients include those with relapsed osteosarcoma among other malignancies, and relevant end points include maximum tolerated dose, toxicities, response rate, progression-free survival, and overall survival. This study, led by the City of Hope, is evaluating the novel concept of combining molecularly targeted and cytotoxic therapies, but is associated with a significant risk for toxicity.
metastatic relapsed osteosarcoma: resectable and unresectable (NCT00617890). Cixutumumab is also a monoclonal antibody to IGF1R and is being studied in children with many different tumor types, including osteosarcoma (NCT00831844).

**mTOR Inhibition**

The mTOR pathway is hypothesized to be involved in many different malignancies, and is a serine/threonine protein kinase that plays a critical role in regulating protein translation necessary for cell growth and survival.\(^{54,55}\) In vitro, inhibition of mTOR induces cytostasis or apoptosis in many cancer cell lines, likely because of its effects on protein translation.\(^{56}\)

Multiple studies are examining the role of mTOR inhibition in sarcomas. The Sidney Kimmel Comprehensive Cancer Center is conducting a phase I/II study to evaluate the safety and efficacy of temsirolimus and liposomal doxorubicin in patients with advanced sarcoma, including osteosarcoma (NCT00949325). Combined IGF-1R and mTOR inhibition is currently being investigated in a phase I/II study with temsirolimus and cixutumumab (NCT01016015).

**Anti–Insulin-Like Growth Factor 1 Receptor Therapy**

The insulin-like growth factor 1 receptor (IGF-1R) pathway has been implicated in the pathogenesis and progression of many malignancies, including osteosarcoma.\(^{48,49}\) Ligand binding to IGF-1R triggers downstream activation of the PI3K/AKT/mammalian target of rapamycin (mTOR) pathway and multiple events resulting in enhanced cell survival proliferation, motility, and invasion.\(^{50}\) IGF-1R is overexpressed in many malignancies, including sarcoma, and inhibition of IGF-1R in vitro has resulted in tumor apoptosis and growth inhibition.\(^{51–53}\)

SARC completed enrollment to a multi-institutional phase II study of R1507, a monoclonal antibody to IGF-1R, which included a cohort of patients with osteosarcoma. Preliminary results are still pending. Multiple studies targeting IGF-1R in osteosarcoma are currently open. An international study of the IGF-1R antibody SCH 717454 is currently enrolling 2 different cohorts of patients with metastatic relapsed osteosarcoma: resectable and unresectable (NCT00617890). Cixutumumab is also a monoclonal antibody to IGF1R and is being studied in children with many different tumor types, including osteosarcoma (NCT00831844).

### Table 2  Select Currently Recruiting Clinical Studies for Patients With Osteosarcoma

<table>
<thead>
<tr>
<th>Trial Name</th>
<th>Drug/Target</th>
<th>NCT Identifier</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combination Chemotherapy, PEG-Interferon-Alfa-2b, and Surgery in Treating Patients with Osteosarcoma (COG-AOST0331, MRC-EURAMOS1)</td>
<td>Biologic</td>
<td>NCT00134030</td>
</tr>
<tr>
<td>Zoledronic Acid and Combination Chemotherapy in Treating Patients With Newly Diagnosed Metastatic Osteosarcoma (COG-AOST06P1)</td>
<td>Osteoclast/melavonate pathway</td>
<td>NCT00742924</td>
</tr>
<tr>
<td>Evaluation Of Zoledronic Acid as a Single Agent or as an Adjuvant to Chemotherapy in High-Grade Osteosarcoma (ZOL)</td>
<td>Osteoclast/melavonate pathway</td>
<td>NCT00691236</td>
</tr>
<tr>
<td>Combination Chemotherapy With or Without Zoledronic Acid in Treating Patients With Osteosarcoma</td>
<td>Osteoclast/melavonate pathway</td>
<td>NCT00470223</td>
</tr>
<tr>
<td>A Placebo-Controlled Study of AZD0530 in Patients With Recurrent Osteosarcoma Localized to the Lung (SARC 012)</td>
<td>Src-kinase</td>
<td>NCT00752206</td>
</tr>
<tr>
<td>Dasatinib, Ifosfamide, Carboplatin, and Etoposide in Treating Young Patients With Metastatic or Recurrent Malignant Solid Tumors</td>
<td>Src-kinase</td>
<td>NCT00788125</td>
</tr>
<tr>
<td>A Study to Determine the Activity of SCH 717454 in Subjects With Relapsed Osteosarcoma or Ewing’s Sarcoma (P04720)</td>
<td>IGF-1R</td>
<td>NCT00617890</td>
</tr>
<tr>
<td>Cixutumumab in Treating Patients With Relapsed or Refractory Solid Tumors</td>
<td>IGF-1R</td>
<td>NCT00831844</td>
</tr>
<tr>
<td>Safety and Efficacy Study of Torisel and Liposomal Doxorubicin in Patients With Recurrent Sarcoma</td>
<td>mTOR</td>
<td>NCT00949325</td>
</tr>
<tr>
<td>Temsirolimus and Cixutumumab in Treating Patients With Locally Advanced, Metastatic, or Recurrent Soft Tissue Sarcoma or Bone Sarcoma</td>
<td>IGF1-R, mTOR</td>
<td>NCT01016015</td>
</tr>
<tr>
<td>Sorafenib in Relapsed High-Grade Osteosarcoma</td>
<td>VEGF, PDGFR, RAF</td>
<td>NCT00889057</td>
</tr>
<tr>
<td>A Study of Bevacizumab in Combination With Chemotherapy for the Treatment of Osteosarcoma (OS2008)</td>
<td>VEGF</td>
<td>NCT00667342</td>
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Abbreviations: IGF, insulin-like growth factor; mTOR, mammalian target of rapamycin; PDGFR, platelet-derived growth factor receptor; VEGF, vascular endothelial growth factor.
mTOR inhibition is being studied in a multicenter phase II study of temsirolimus and cixutumumab (NCT01016015). The pathways are hypothesized to have a potentially critical interaction in the proliferation of cancer cells, which has been supported by multiple preclinical studies.\textsuperscript{57–59} Multiple cohorts of advanced sarcoma are being studied, including IGF-1R–positive bone sarcoma.

**Antivascular Endothelial Growth Factor Receptor Therapy**

Targeting angiogenesis through blockade of vascular endothelial growth factor receptor (VEGFR) has been successful in improving the outcomes of patients with many malignancies, including hepatocellular carcinoma, renal cell carcinoma, lung carcinoma, and colorectal carcinoma. VEGF expression has been implicated as a negative prognostic factor in osteosarcoma and thus has been implicated as an important signaling pathway.\textsuperscript{60,61} The multi–kinase inhibitor sorafenib has been shown in vitro and in vivo to have antitumor activity and antiangiogenic effects. Sorafenib blocks the receptor tyrosine kinases VEGFR, PDGFR, and RAF. In vitro, sorafenib inhibits osteosarcoma cell-line proliferation and was shown to induce apoptosis and down-regulate P-ERK1/2, MCL-1, and P-ERM, which led to further apoptosis.\textsuperscript{62} The Italian Sarcoma Group is currently conducting a phase II trial of sorafenib in refractory advanced osteosarcoma (NCT00889057).

VEGFR is also being targeted in osteosarcoma therapy in a multicenter study led by St. Jude Children’s Research Hospital (NCT00667342). In this trial, bevacizumab, a monoclonal antibody to VEGF, is being used to treat localized or metastatic osteosarcoma. This single-arm study is being conducted to examine the safety and efficacy of adding bevacizumab to standard chemotherapy agents of cisplatin, doxorubicin, and methotrexate for localized disease, and cisplatin, doxorubicin, methotrexate, ifosfamide, and etoposide for metastatic disease. This trial is particularly appealing given the success observed in adding bevacizumab to standard chemotherapy for treating other malignancies.

**EWS Family of Tumors**

EWS family of tumors are high-grade neoplasms that most often originate in the bone, although they can arise in soft tissues. Front-line therapy for this disease consists of intensive chemotherapy, including the standard cytotoxic agents doxorubicin, vincristine, cyclophosphamide, actinomycin D, ifosfamide, and etoposide. Trials incorporating a regimen of multiagent chemotherapy and local control with surgery or radiation have resulted in improved overall survival rates of 10% to 15% up to 60% to 70% in patients with localized disease.\textsuperscript{63} Patients with metastatic disease continue to have an overall survival rate of approximately 25%.

Despite the successes of front-line therapy, similar to osteosarcoma, the management of patients with refractory or relapsed disease remains challenging. Although effective second-line cytotoxic chemotherapy exists, response rates are lower than with front-line therapy, and eventually cumulative toxicities or progressive disease require discontinuation of treatment. Commonly used regimens for relapsed disease include ifosfamide/carboplatin/etoposide, cyclophosphamide/topotecan, and temozolomide/irinotecan.\textsuperscript{64–68}

In refractory disease, an obvious target for therapy is the EWS fusion protein EWS-FLI1. Most EWS are associated with a translocation of either EWS-FLI1 (t[11:22]) or EWS-ERG (t[21:22]) in approximately 90% and 10% of cases, respectively.\textsuperscript{69–71} Although cytotoxic chemotherapy can be effective, a targeted approach aimed at this fusion protein, which acts as a transcriptional activator, is strongly desired.\textsuperscript{72–74} Unfortunately, no major breakthroughs have occurred in the direct inhibition of this chimeric protein in humans, but ongoing trials using alternatively strategies are promising (Table 3).

**IGF-1R inhibition**

One of the most promising strategies in EWS is IGF-1R inhibition. Preclinical studies have indicated that IGF-1R activation is instrumental in the malignant transformation of fibroblasts to EWS mediated by EWS-FLI1.\textsuperscript{75} In vitro, in vivo, and early-phase studies have indicated great promise for this class of compounds in EWS.\textsuperscript{76–79} The development of anti-IGFR-targeted therapies in the laboratory and clinic has been reviewed extensively elsewhere.\textsuperscript{80} SARC recently completed accrual to an international multicenter trial of the IGF-1R monoclonal antibody R1507 in multiple sarcomas, including EWS. Preliminary data presented at the 2009 ASCO annual meeting showed evidence of clinically significant responses in patients with EWS.\textsuperscript{81} Currently
recruiting studies include a phase II study of SCH 717454, an anti–IGF-1R fully human monoclonal antibody, for patients with relapsed EWS to assess response rate (NCT00617890). This same drug is being studied with a combination of 1 of 3 combinations of cytotoxic chemotherapy in a phase I/IB study for pediatric patients with advanced solid tumors, including EWS (NCT00960063).

Another phase II study is evaluating the 12-week progression-free survival rate of a cohort of patients with EWS treated with the anti–IGF-1R antibody cixutumumab (NCT00668148). This drug is also being studied in pediatric patients (NCT006914) and in combination with temsirolimus in IGF-1R–positive bone sarcoma (NCT01016015). These trials will help delineate the role of anti–IGF-1R therapy in EWS and perhaps lead to additional studies evaluating the role of cixutumumab earlier in the disease course.

**Immune Therapy**

In addition to being implicated in the pathogenesis of EWS, the EWS-FLI1 chimeric protein may serve as a potential antigen that can be targeted in immune strategies to treat the disease. Currently, multiple ongoing studies using immunotherapy include EWS as a potential histology (Table 3). The National Cancer Institute (NCI) is sponsoring a study for patients with recurrent disease using an individual patient tumor vaccine in combination with chemotherapy and lymphocyte infusion to try to induce an immune response (NCT00923351). Additional approaches used in other recruiting studies include irradiated donor lymphocyte infusions and donor natural killer cell infusions (NCT00640796).

**High-Dose Therapy**

Because EWS is both chemo- and radiosensitive, many attempts and continuing efforts have been made to see what impact high-dose therapy can have on this disease. Completed studies have failed to result in improved survival and have been associated with significant toxicities.82–84

EURO-EWING 99 is a large international, randomized, phase III trial incorporating high-dose therapy for patients with newly diagnosed localized or metastatic EWS (NCT00020566). After initial induction chemotherapy and local therapy, patients undergo risk-stratified consolidation therapy (Figure 1). Patients who experience poor response (R2) are randomized to undergo either additional standard cytotoxic therapy and whole lung irradiation if incompletely resectable disease remains, or high-dose
therapy with busulfan, melphalan, and peripheral blood stem cell transplant along with concurrent radiation if unresectable disease remains. EWING 2008 is a joint protocol randomizing patients experiencing good response to standard therapy plus the addition of either fenretinide; zoledronic acid; fenretinide plus zoledronic acid; or no add-on treatment (NCT00987636). An additional randomization assigns very high-risk (R3) patients to standard chemotherapy versus high-dose therapy with treosulfan-melphalan with autologous stem cell support and additional chemotherapy. The hope is that this large randomized study will help determine the role of peripheral blood stem cell transplant in EWS.

A smaller phase II NCI study is evaluating the role of allogeneic/syngeneic stem cell transplantation along with concurrent radiation in EWS, poor histologic response and primary pulmonary metastases; and R3: metastatic EWS to bone/bone marrow at diagnosis. Abbreviations: A, actinomycin D; Bu-Mel, high-dose therapy with busulfan-melphalan with stem cell support; C, cyclophosphamide; D, doxorubicin; E, etoposide; I, ifosfamide; ME-ME, high-dose therapy with melphalan-etopophos with stem cell support if prior irradiation of axial sites; Treo-Mel, high-dose therapy with treosulfan-melphalan with stem cell support and 8 additional cycles of vincristine, actinomycin D, and cyclophosphamide; V, vincristine. Adapted from Dirksen U, Jurgens H. EWING 2008: Darstellung der Studie. Available at: http://euro-ewing.uni-muenster.de. Accessed March 31, 2010.

**Figure 1** Euro-Ewing-99 Schema. Patients are risk-stratified into R1: localized Ewing’s sarcoma (EWS), good histologic response; R2: localized EWS, poor histologic response and primary pulmonary metastases; and R3: metastatic EWS to bone/bone marrow at diagnosis. Abbreviations: A, actinomycin D; Bu-Mel, high-dose therapy with busulfan-melphalan with stem cell support; C, cyclophosphamide; D, doxorubicin; E, etoposide; I, ifosfamide; ME-ME, high-dose therapy with melphalan-etopophos with stem cell support if prior irradiation of axial sites; Treo-Mel, high-dose therapy with treosulfan-melphalan with stem cell support and 8 additional cycles of vincristine, actinomycin D, and cyclophosphamide; V, vincristine.

**Chondrosarcoma**

Unlike the 2 other most common bone sarcomas, chondrosarcoma tends to be a low- to intermediate-grade malignancy that predominantly affects older individuals. Of these malignancies, 90% are conventional chondrosarcomas, which have a low metastatic potential and are primarily managed with surgical resection. Unfortunately, once conventional chondrosarcomas metastasize, no effective systemic therapy exists. Experts hypothesize that this may be because of the indolent growth pattern of chondrosarcoma, rendering it relatively insensitive to cytotoxic therapies, which are typically effective in rapidly dividing cells. Alternatively, the relatively impermeability of the chondrosarcoma extracellular matrix and low vascularity of these malignancies may limit penetration of systemic therapy.85

Given the relatively low incidence of chondrosarcoma, it is not surprising that relatively few trials exist specific to this malignancy. Final results are pending of several recently completed trials, which specifically included cohorts of patients with chondrosarcoma. These studies include phase II studies of gemcitabine/docetaxel (SARC), pemetrexed (Southwest Oncology Group), and perifosine (SARC). One actively recruiting trial is studying the efficacy of imatinib, the multi–tyrosine kinase inhibitor to PDGFRα/β, KIT, and BCR-ABL in patients with chondrosarcoma and desmoid tumor. Both PDGFRα and PDGFRβ are expressed in con-
necessary to achieve clinical benefit. Proton therapy has been used to help achieve local control of chondrosarcomas, particularly in the skull base, a location where it is difficult to achieve adequate surgical control. Two clinical trials are currently being conducted examining the use of proton-beam radiation for patients with chondrosarcomas of the skull base and/or spine, which are particularly appealing for patients with this uncommon but challenging disease (NCT00496522 and NCT00788125).

Less-common subtypes of chondrosarcoma include mesenchymal chondrosarcoma, extraskeletal myxoid chondrosarcoma (considered a soft tissue sarcoma), and dedifferentiated chondrosarcoma. Because their biology and clinical behavior are different from those of conventional chondrosarcomas, candidate patients should be guided to trials most relevant to their histology.

**Conclusions**

Bone sarcomas are a challenging and diverse group of malignancies. Laboratory research has identified several candidate therapeutic targets for these diseases, ranging from IGF-1R inhibition to VEGF blockade. Multiple ongoing clinical trials share the common goal of advancing the care of patients with bone sarcomas.
References


Bone Sarcoma Therapies


