Published in final edited form as:

Curr Oncol Rep. 2008 July ; 10(4): 350–358. doi:10.1007/s11912-008-0054-3.

Novel Targets With Potential Therapeutic Applications in Osteosarcoma

Chand Khanna, DVM, PhD

National Institutes of Health, National Cancer Institute, Pediatric Oncology Branch, Tumor Metastasis Biology Section, 37 Convent Drive, Bethesda, MD 20892, USA.

Abstract

For patients with osteosarcoma, the development of metastases, often to the lungs, is the most common cause of death. Long-term outcomes for patients who present with localized or disseminated disease have largely remained unchanged over the past 20 years. Further improvements in outcome are not likely to come from intensification of cytotoxic chemotherapy; as such, new targets for treatment are needed. A view toward such targets in osteosarcoma may be constructed based on three common clinical features of the disease. These include the origin of osteosarcoma in the bone or primitive mesenchymal cells, the predictable process of metastatic progression characterized by this disease, and the development of metastatic lesions almost exclusively in the lung. It is likely and potentially favorable for some targets to be relevant for more than one process. This review summarizes novel targets under evaluation for the treatment of osteosarcoma based on these three features of the disease.

Introduction

The cause of death for the vast majority of cancer patients is the development of metastases at sites distant from that of the primary tumor. For pediatric osteosarcoma patients, despite successful management of the primary tumor through multimodality approaches, the development of metastases, often to the lungs, is the most common cause of death [1•,2,3]. Strategies for managing the primary tumor have advanced to the extent that local failure in osteosarcoma patients with nonaxial tumors is rare. Significant improvements in long-term outcome for patients presenting with localized disease improved in the 1980s, when adjuvant single-agent chemotherapy was added to surgical control of the primary tumor. Subsequent intensification of chemotherapy and the use of multimodality approaches further improved long-term outcomes for patients. By 1990, approximately 65% of patients presenting with localized disease were cured with conventional therapy. Unfortunately, since that time, long-term survival for these patients has remained largely unchanged [1•]. Even more disappointing is that no survival improvements have been seen for those patients who

Corresponding author Chand Khanna, DVM, PhD, National Institutes of Health, National Cancer Institute, Pediatric Oncology Branch, Tumor Metastasis Biology Section, 37 Convent Drive, Bethesda, MD 20892, USA, khannac@mail.nih.gov.

Disclosure

This work was prepared as part of Dr. Khanna's official duties as a National Institutes of Health employee.

present with metastatic disease; less than 30% of these patients survive. As such, new treatments are needed.

The search for osteosarcoma-specific targets through the study of genetic aberrations or gene expression studies using osteosarcoma tissues has not identified common and reproducible genetic lesions [4,5]. Osteosarcoma is characterized by a complex and bizarre karyotype without the consistent, recurring translocations often seen in other sarcomas. In fact, the most consistent genetic finding in osteosarcoma, beyond dysregulation of p53 and RB (retinoblastoma), is significant aneuploidy [6]. This has suggested the possibility of an early defect in chromosomal stability or DNA repair/surveillance as a mechanism for osteosarcomagenesis and the resultant bizarre aneuploidy that is devoid of consistent genetic aberrations across patients [7–9].

In the absence of such consistently defined genetic aberrations, one approach toward therapeutic targeting in osteosarcoma may be based on common clinical features of the disease. First, the tumor is believed to originate either from mesenchymal cells resembling osteoblasts or osteoblasts themselves. Second, osteosarcoma is characterized by the process of metastatic progression. Third, there is development of metastatic lesions—almost always in the lung—that are not responsive to most current therapies.

This review summarizes novel therapeutic targets under discovery and development for osteosarcoma, based on these three features of the disease. Table 1 provides a summary of several osteosarcoma targets, including those discussed below, and outlines their status in the developmental path. Several targets presented in this review may have overlap among the three discussed clinical features of osteosarcoma. These may be of additional value as therapeutic targets in osteosarcoma.

Osteosarcoma Targets

Mesenchymal Cells and Bone Biology

Historically, it has been suggested that the cell of origin for most osteosarcoma cells is the osteoblast or an osteoblast progenitor. This prediction has been based on the location of primary tumor development (ie, bone) and the fact that molecular and protein analyses of osteosarcoma samples reveal a strong bone phenotype. Recent studies have provided data to suggest that primitive cells of mesenchymal origin, often described as mesenchymal stem cells, may represent the cellular target for transformation (ie, cell of origin) in osteosarcoma. This hypothesis would suggest that the transforming event that occurs in mesenchymal stem cells drives this cancer toward a bone-like phenotype. Irrespective of the actual cell of origin, it is commonly agreed that the expression genotype and the cellular phenotype of osteosarcoma are related to bone and may lead to novel therapeutic opportunities [10]. The following subsection summarizes potential treatment targets for osteosarcoma that have been suggested, in part, based on this bone connection. Examples in Table 1 are meant to reflect targets relevant to the osteosarcoma bone/mesenchymal phenotype rather than merely targets of a primary tumor.

Potential targets linked to bone/mesenchymal phenotype

Insulin-like growth factor and insulin-like growth factor receptor: The growth and development of the adult skeleton is largely the result of growth hormone–induced release of insulin-like growth factor 1 (IGF-1), primarily from the liver, and its interaction with IGF-1 on osteoblasts and other supporting cells [11]. Proliferation and survival of normal and malignant cells is linked to IGF-1 receptor activation. Amplification and/or activating mutations in the IGF-1 receptor have not yet been found in osteosarcoma tumors to date; nonetheless, both preclinical and clinical studies suggest the importance of this pathway in osteosarcoma.

Targeting the IGF-1 ligand in cancer has shown promise in several cancer types [12]. Blockade of growth hormone release and consequent partial suppression of serum IGF-1 using octreotide was evaluated in early-phase human studies; however, it was not pursued, in part due to the lack of activity in preclinical studies in dogs with naturally occurring osteosarcoma [13]. The persistence of high local (microenvironment) expression of IGF-1, despite suppression of serum IGF-1, in the primary tumor and metastatic lesions in treated dogs may explain the lack of therapeutic benefit derived from efforts to target the IGF-1 ligand [14]. Recent opportunities to target the IGF-1 receptor have been possible through humanized antibodies that target the IGF-1 receptor and small molecule inhibitors directed against the IGF-1 receptor kinase [15••]. A number of antibodies targeting the IGF-1 receptor are in various stages of preclinical and clinical development in cancers including osteosarcoma, and have been associated with single-agent activity in preclinical models [16•] Even more exciting has been anecdotal evidence found in early human clinical trials of activity for these agents in patients with sarcoma. These dramatic responses in patients suggest a unique dependence or addiction for sarcoma cells that express the IGF-1 receptor. The determinants of responsiveness to IGF-1 receptor inhibitors are not yet understood.

The recent availability of therapeutic agents that may target this receptor and pathway, including IGF-1 receptor antibodies and small molecule inhibitors of the IGF-1 receptor kinase, has provided an opportunity to evaluate the presumed dependence of sarcomas on this growth factor pathway in the clinical setting. It is likely that additional agents targeting proximate downstream components of the IGF-1 receptor pathway, including inhibitor of phosphoinositide 3 (PI3) kinase and AKT kinase, also will become clinically available for future approaches using multiple agents that target this pathway.

Osteoclast activation: Although the transformed cell in osteosarcoma is generally believed to be an osteoblast or osteoblast-like cell, the interaction (cross-talk) between osteoclasts and osteoblasts has been demonstrated in bone and in osteosarcoma [17]. The receptor activator for nuclear factor κ -B (RANK) ligand–osteoprotegerin axis is the primary pathway associated with osteoclast activation. It may contribute to the biology of osteosarcoma through the osteoclast cross-talk to malignant osteoblasts and the resultant release of bone-associated growth factors in the microenvironment of the bone lesion [18].

Much of the drug development focus for bisphosphonates stems from the role of the activated osteoclast in osteoporosis. However, development efforts have increasingly included bone metastases [18]. Bisphosphonates act by blocking the RANK–RANK ligand

interaction [19]. Second-generation or aminobisphosphonates (ie, zoledronate) may also be useful due to potent RANK inhibition and indirect inhibition of the Ras signaling pathway. As such, direct cytotoxic and antiangiogenic activities have also been associated with the aminobisphosphonates [20]. Aminobisphosphonates have been shown to be active in preclinical models of osteosarcoma lung metastasis [21]. Phase 2 feasibility studies have confirmed safety with pamidronate in osteosarcoma patients. Phase 3 studies have shown that clodronate prevents new metastases in breast cancer patients. An interesting clinical outcome in these studies was the reduction in both bone and soft tissue metastases [22,23]. Bisphosphonate therapy may disrupt the bone marrow environment, resulting in reduction of metastatic colonies in the marrow and a resultant reduction in eventual soft tissue metastases that emerge from this bone marrow site of dormancy (see below). Although hypothetical, it is reasonable that the observation of cancer cells in the bone marrow of nearly 63% of osteosarcoma patients could lead to a similar clinical benefit in pulmonary metastasis in osteosarcoma [24]. Plans are under way to initiate a phase 2 study of zoledronate combined with conventional chemotherapy in children with metastatic osteosarcoma.

It is unlikely that the daily treatment schedules used successfully in currently reported preclinical metastasis models will be achievable in human studies without toxicity [22]. As such, it is unclear whether less intensive schedules will be successful. Plans are currently under way to define the activity of less intensive schedules in dogs with osteosarcoma treated with conventional chemotherapy and aminobisphosphonates as an adjuvant to surgery (personal communication, Tim Fan, University of Illinois).

Notch: The importance of the Notch signaling pathway has been seen in mesenchymal stem cells, skeletal development, and in normal bone [25,26]. The Notch pathway consists of a series of receptors including Jagged, Delta, and Notch. Through these receptors, Notch signaling results in activation of the HES transcription factor. Ligands and receptors in the Notch signaling pathway and downstream targets, including HES, are expressed in osteoblasts and osteosarcoma cells [26].

Therapeutic opportunities that may emerge from disruption of the Notch signaling pathway include agents that may block sheddase enzymes, which act to prevent intracellular activation of Notch receptors [27]. Additional opportunities may include blocking interactions between Notch ligands (ie, Delta-like 4) and the Notch receptors [28]. The study of the Notch signaling pathway in sarcoma and osteosarcoma and the development of specific inhibitors of the Notch pathway as a cancer treatment are under way.

Osteosarcoma Targets: Metastatic Progression

As previously discussed, metastasis is a consistent and fundamental feature of osteosarcoma biology that is responsible for most patient mortality. Because most patients present with localized disease that is effectively managed with multimodality therapy, the development of metastasis must involve the dissemination of microscopic metastatic cells, present at diagnosis, that eventually progress to grossly detectable metastases despite adjuvant therapy. Based on the work of several groups, it is likely that this process of metastasis involves microscopic tumor cells leaving the primary tumor through a well-regulated lysis of

surrounding stroma. These cells pass through the tumor basement membrane through or between endothelial cells to enter the circulation (intravasation). While in the circulation, tumor cells must resist anoikis (programmed cell death associated with loss of cellular contact), evade immune recognition and physical stress, and eventually arrest at distant organs. At that distant site, the cell must leave the circulation (extravasation), survive in the hostile microenvironment of a foreign tissue site, proliferate, create new blood vessels (angiogenesis) or co-opt existing blood vessels, and then successfully grow into a measurable metastatic lesion. In patients with osteosarcoma, metastasis shares the features of hematogenous spread and high predilection for the lung. Given that these metastatic processes are likely to be similar in many cancers, an important opportunity for preclinical and clinical studies in osteosarcoma will be the assessment of agents that may be in development or in clinical use for other indications. It is likely that, based on the stage of development and human experience, the need for osteosarcoma-specific preclinical efficacy data will be small. Rather, a focus on safety in the pediatric and adolescent population will be needed.

Several metastatic processes have served as targets for the development of new cancer treatments [29]. Important among these is the ability of tumor cells, particularly metastatic tumor cells, to evade immune detection. The targeting, activation, and modulation of the immune system is broadly referred to as immunotherapy (reviewed elsewhere [30]). The most recently completed US Intergroup phase 3 clinical trial in osteosarcoma patients evaluated a form of immunotherapy, liposomal muramyl tripeptide phosphatidyl ethanolamine (L-MTP-PE), in combination with existing cytotoxic treatments [31]. Although still controversial, recent assessment of survival outcomes in this randomized study support the clinical benefit of this form of immunotherapy [32•]. Beyond immunotherapy, the following subsection summarizes two potential metastatic process targets that may be considered for osteosarcoma. Additional targets related to the metastatic cascade are summarized in Table 1. Because the process of metastasis leads to metastatic lesions, many targets will overlap between these two osteosarcoma characteristics.

Potential targets linked to the metastatic process

Angiogenesis—It is now universally accepted that the development of new blood vessels from endothelial progenitors (vasculogenesis) or from existing blood vessels (angiogenesis) is required for cancer progression [33]. Angiogenesis is the most successfully targeted process that defines the metastatic cascade of cancer. The growth and progression of sarcomas has been consistently connected with angiogenesis [34]. Antiangiogenic and vascular-targeting agents have been in clinical trials for some time, and many of these are beginning to be assessed in early-phase trials in osteosarcoma patients [35].

High expression of vascular endothelial growth factor (VEGF) and VEGF receptor (VEGFR) in osteosarcoma tissues and their correlation with poor prognosis suggests that the evaluation of antibodies against VEGFR or small molecule inhibitors of VEGFR kinase is reasonable [34]. Predictably, preclinical studies with an inhibitor of VEGFR kinase (AZD2171) have been effective against osteosarcoma xenografts [36].

There are strong and overlapping data connecting the metastatic phenotype of osteosarcoma with prolific angiogenesis. The complexity of the angiogenic phenotype suggests a strong likelihood that single-agent inhibitors of a single component of this angiogenic phenotype (ie, VEGFR inhibition) will not be sufficient to control metastatic progression alone. Furthermore, the hypothetical lack of resistance associated with antiangiogenic therapy has not proven itself to be true in the clinic and in more complex preclinical models of cancer [37,38]. Collectively, and not surprisingly, combinations of antiangiogenic agents or combinations of antiangiogenic agents with other treatments will be necessary.

c-MET—c-MET is the receptor for hepatocyte growth factor (HGF). Aberrant signaling resulting from either c-MET or HGF overexpression has been linked to the development of cancer in murine models [39]. Furthermore, preclinical studies in vitro and in vivo support the role of c-MET signaling in cancer progression and specifically metastasis. c-MET has been shown to be expressed in osteosarcoma primary tumors and metastatic lung nodules [40]. In fact, c-MET was first identified as an oncogene in chemically transformed human osteosarcoma cells. It is likely that several metastatic processes are linked to c-MET signaling, including cell motility, invasion, proliferation, and survival [39].

Because c-MET is a growth factor receptor with an intracellular signaling domain with tyrosine kinase activity, the development of small molecule inhibitors of c-MET has been possible. In preclinical models, several potent and both highly specific and less specific tyrosine kinase inhibitors of c-MET have been developed and shown to be active against metastatic progression [41]. The inhibition of c-MET has been effective in suppressing the metastatic phenotype in osteosarcoma cells [42]. Human clinical trials have been slow to develop, in part because of the belief that c-MET inhibitors would have greatest utility in the setting of microscopic disease, and in part due to the limited opportunity to study this biology in early human clinical trials. However, recent data suggest the value of c-MET inhibition against measurable disease. They also suggest a unique dependence or addiction for c-MET signaling in metastatic lesions that is not observed in the primary tumor, thus supporting the need for innovative early-phase human trial designs [43,44].

The expression of c-MET in osteosarcoma and evidence linking its inhibition with a suppressed metastatic phenotype are very encouraging. The evaluation of this agent in an appropriate and informative patient population is necessary to prevent a false negative (type II error) result from these studies.

Is it too late since the horse is already out of the barn?: Because many of the cellular processes associated with metastasis have already occurred when a patient presents, some may argue that therapeutic targeting of these events may be too late. Our understanding of events and the timing of events leading to metastatic progression are far from complete; accordingly, such speculation is risky. For example, it is unclear if microscopic cells that leave the primary tumor early in the development of osteosarcoma move directly to the lung and reside in the lung for long periods of time (dormancy) or if these cells transit from the primary tumor to “protected environments” (ie, the bone marrow) where they undergo dormancy and then move through all the steps of metastasis en route to the lung. Similarly, it is reasonable that the cells capable of completing the complex set of events required for

metastasis will continue to metastasize to yet distant sites (within the lung in osteosarcoma). Indeed, if metastatic cells emerge from “protected sites” and if metastatic lesions continue to metastasize, the opportunity to improve patient outcomes by targeting the process of metastasis would have merit not only in patients who present with localized and presumed microscopic metastasis, but also in patients with gross metastasis. Shortcomings in our understanding of the biology of metastasis preclude any a priori judgments on the value of agents that target metastatic processes. However, rigorous preclinical studies and innovative clinical trial designs will be necessary to allow the assessment of these agents in patients.

Osteosarcoma Targets

Established Metastatic Lesions

It is unfortunate that the process of metastasis and the resulting metastasis (ie, the metastatic lesion) have the same name. The verb and the noun describe very different biological and clinical conditions that should be considered as distinct entities. Although clearly related, the verb refers to a set of stepwise cellular processes that result in the dissemination of tumor cells from the primary tumor site to distant secondary sites. The process, summarized above, includes migration, invasion, entry into the circulation, and eventual arrest and extravasation at a distant secondary site. The noun refers to either the single metastatic cell or the gross metastatic lesion at the secondary site of a patient. The focus of most basic research in the field of metastasis is on the process of spread. This focus overlooks the fact that patient mortality is the result of the metastatic lesions. Therapeutic targets within these lesions may be distinct from the therapeutic targets associated with the process of metastasis or the primary tumor. Beyond this, it is furthermore unclear whether primary tumors and metastatic lesions are equally responsive to chemotherapeutic agents or to targeted anticancer agents. In osteosarcoma, unlike most other cancers, the resection of pulmonary metastatic nodules—when possible—is the first-line treatment for recurrent patients. Metastectomy is associated with 5-year survival rates of 35% in patients who achieve complete surgical remission. Subsequent relapses may also be successfully treated with metastectomy, although at decreasing survival rates. The resistance of these pulmonary metastases to currently available systemic therapy is common. The failure of treatment may be the result of acquired resistance to chemotherapy [45] and/or to the ability of metastatic cells to develop “protection” within their microenvironment in the lung [46]. As such, methods to address chemotherapy resistance and target the metastatic lesion within the context of its microenvironment may be considered for the management of patients. The following subsection summarizes potential targets linked to the maintenance of established metastatic lesions and communication with the microenvironment in osteosarcoma. Additional targets related to the metastases are summarized in Table 1.

Potential targets linked to established metastatic lesions

Mammalian target of rapamycin: Mammalian target of rapamycin (mTOR) is a critical node in a signaling pathway that connects many growth factor receptors, through intermediaries including AKT and mitogen-activated protein kinase, to the cytoskeleton and translational machinery of the cell. As a result, mTOR is able to convert signals that sense the nutritional and stress status of a cell (in the cell’s microenvironment) into specific

proteins that can manage the stress. Cancer cells are highly dependent on the targets of mTOR-mediated translation, specifically through cap-dependent translation through eIF4E/4EBP1. Many of the known translational targets of mTOR have been connected to cancer, including c-myc, VEGFR, hypoxia-inducible factor, and transforming growth factor- β . That mTOR may be an important target for osteosarcoma is also supported by mTOR's importance in mesenchymal stem cell and bone biology [47].

Rapamycin, an approved agent useful in the setting of immunosuppression for transplant, directly inhibits mTOR and, as such, prevents downstream expression of mTOR targets. Rapamycin and newly developed analogues (rapalogues) have been evaluated in preclinical and human clinical studies in a number of cancers, including osteosarcoma [48]. We have connected the metastasis-associated protein ezrin with activation of the mTOR pathway in osteosarcoma, and furthermore found that rapamycin, and its blocked ester (rapalogue CCI779), reduced metastases in a murine model of osteosarcoma [49,50]. In unpublished data from our laboratory, it also appears that rapamycin disrupts existing metastatic lesions in murine models. Early human clinical data with rapalogues support the therapeutic value of targeting mTOR in osteosarcoma.

The therapeutic targeting of mTOR with rapamycin and rapalogues in osteosarcoma is strong. Given the multiplicity of effects related to the inhibition of mTOR (ie, immunosuppression and anticancer), it is likely that optimal schedules for treatment will be required for the complete success of these agents to be seen. It is also likely that the observation of increased phosphorylation of AKT following mTOR suppression with rapamycin will require additional consideration and potential combinations with agents that may act at, or upstream of, AKT (eg, IGF-1 receptor inhibition).

Heat shock protein 90: Heat shock protein 90 (Hsp90) is a molecular chaperone of specific "client" proteins that in many cases are linked to oncogenic and metastatic cancer phenotypes [51]. In many cases, Hsp90–client protein interactions protect these proteins from degradation. Physiologic protection of specific proteins is believed to have emerged as a means to overcome short-term cellular stressors. In cancer and specifically metastases, these cellular stressors are experienced as chronically related to vacillating tumor hypoxia, atypical growth factor signals in the foreign microenvironment, and relative nutrient deprivation [52]. It may be that the ability of metastatic cancers to survive the metastatic process results from an ability to manage these stressors. As a result, metastatic cancer cells are more highly dependent on Hsp protection of client proteins than are primary tumors or normal tissues.

Preclinical data support the fact that Hsp90 inhibition results in impaired cell growth, apoptosis, and angiogenesis suppression, presumably through degradation of client proteins previously protected by Hsp90 [53]. The classic Hsp inhibitor is geldanamycin (GA), a benzoquinone ansamycin. GA, its analogues, and its derivatives have entered early-phase human studies and shown reasonably low toxicity at exposures that can disrupt Hsp90 stabilization of client proteins [53]. Interestingly, many of these client proteins, such as IGF-1 receptor, AKT, and c-MET, may have specific relevance to osteosarcoma.

Newer-generation inhibitors of Hsp90 are in preclinical and clinical development. Improvements in these agents include specific binding of Hsp90, improved competition with client proteins, reduced toxicity, and improved pharmacokinetics.

Barriers to Progress

Although the list of targets available for the potential treatment of osteosarcoma patients is already long and provides a basis for optimism, several factors, related and unrelated to the biology of this aggressive disease, must be addressed before improvements in long-term patient outcomes can occur. A limited number of patients are diagnosed with osteosarcoma each year. As a result, only a single, multicenter, international phase 3 trial including a new agent can be launched in osteosarcoma every 4 to 8 years. Accordingly, creativity in study design and use of the data is needed. The predictable pattern of metastasis to the lungs seen in osteosarcoma patients provides a unique opportunity to evaluate novel agents that target the metastatic lesions in the lung or prevent further metastatic progression. In parallel, an important translational gap, characterized by access to patient tissues, cell lines, and animal models, must be filled to move forward these novel targeted agents in trials for osteosarcoma patients.

The Children's Oncology Group has addressed the issue of patient tissue collection through the development of an osteosarcoma biospecimen repository. Partnering foundations have identified shortcomings in the delivery and sharing of these biospecimen reagents and are developing streamlined approaches to provide biostatistical support in the use of these clinical materials (<http://www.quadw.org>). Improvements in access, annotation, and biostatistical support are expected to increase the utility of tissue resource through these efforts. An innovative preclinical drug-screening program has been initiated through the support of the National Cancer Institute's (NCI) Cancer Therapeutics Evaluation Program for pediatric malignancies, including osteosarcoma. This initiative, referred to as the Pediatric Preclinical Testing Program (PPTP; <http://pptp.stjude.org>) has begun rigorous in vivo evaluation of novel agents provided by the pharmaceutical industry in panels of sarcoma xenograft models. This effort should identify agents currently in clinical development that may have activity in osteosarcoma.

Preclinical studies in naturally occurring osteosarcoma that develop in dogs have become integrated within the drug development process through the Comparative Oncology Trials Consortium (<http://ccr.cancer.gov/resources/cop/COTC.asp>). This newly formed and NCI-initiated consortium is now able to evaluate potentially active osteosarcoma agents in relatively short times given the 10 to 100 times greater prevalence of osteosarcoma in dogs compared with pediatric patients [54•]. It is hoped that these collective preclinical strategies and opportunities can identify agents with the greatest potential to improve outcome and prioritize them for consideration in early innovative human clinical trials.

Finally, an unexpected barrier to advancement in the field is the relative success seen in the management of osteosarcoma patients who present with localized disease. The result of this success, defined by cure of more than 65% of patients using conventional treatments, is a conservative approach toward the addition of new agents. This conservatism is based on

concerns that a new agent may diminish the efficacy of standard chemotherapy agents or that unique toxicities may compromise established treatment schedules. Accordingly, it is imperative that we improve upon current methods to prospectively identify the 35% of patients who will fail conventional treatment. Once we can correctly predict poor prognosis, less conservative treatment options and potentially active agents can be considered for these high-risk populations.

Conclusions

Advances in our understanding of bone biology, the mesenchymal/stem cell origins of osteosarcoma, and the process of metastasis have uncovered many targets of potential value to osteosarcoma patients. A preclinical infrastructure for assessing these targets and related therapeutic reagents is emerging to inform early human clinical trials. Continued efforts to identify patients with osteosarcoma at greatest risk for treatment failure who may receive novel therapies in creative clinical trial designs are under way. This will allow these agents to be assessed quickly and integrated in the management of patients who present with localized or disseminated osteosarcoma.

Acknowledgment

The author would like to thank Drs. Joseph Briggs, Su-Young Kim, and Richard Gorlick for assistance in the preparation and review of this manuscript.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- Of importance

- Of major importance

1. Ferrari S, Palmerini E: Adjuvant and neoadjuvant combination chemotherapy for osteogenic sarcoma. *Curr Opin Oncol* 2007, 19:341–346. [PubMed: 17545797] • A recent report of treatment standards in osteosarcoma.
2. Bruland OS, Pihl A: On the current management of osteosarcoma. A critical evaluation and a proposal for a modified treatment strategy. *Eur J Cancer* 1997, 33:1725–1731. [PubMed: 9470825]
3. Harris MB, Gieser P, Goorin A M, et al.: Treatment of metastatic osteosarcoma at diagnosis: a Pediatric Oncology Group Study. *J Clin Oncol* 1998, 16: 3641–3648. [PubMed: 9817286]
4. Atiye J, Wolf M, Kaur S, et al.: Gene amplifications in osteosarcoma-CGH microarray analysis. *Genes Chromosomes Cancer* 2005, 42:158–163. [PubMed: 15540165]
5. Khan J, Wei JS, Ringner M, et al.: Classification and diagnostic prediction of cancers using gene expression profiling and artificial neural networks. *Nat Med* 2001, 7: 673–679. [PubMed: 11385503]
6. Ladanyi M, Gorlick R: Molecular pathology and molecular pharmacology of osteosarcoma. *Pediatr Pathol Mol Med* 2000, 19: 391–413.
7. Al-Romaih K, Somers GR, Bayani J, et al.: Modulation by decitabine of gene expression and growth of osteosarcoma U2OS cells in vitro and in xenografts: identification of apoptotic genes as targets for demethylation. *Cancer Cell Int* 2007, 7:14. [PubMed: 17845729]
8. Selvarajah S, Yoshimoto M, Maire G, et al.: Identification of cryptic microaberrations in osteosarcoma by high-definition oligonucleotide array comparative genomic hybridization. *Cancer Genet Cytogenet* 2007, 179:52–61. [PubMed: 17981215]

9. Gorlick R, Anderson P, Andrulis I, et al.: Biology of childhood osteogenic sarcoma and potential targets for therapeutic development: meeting summary. *Clin Cancer Res* 2003, 9:5442–5453. [PubMed: 14654523]
10. Spangler JG: Bone biology and physiology: implications for novel osteoblastic osteosarcoma treatments? *Med Hypotheses* 2008, 70: 281–286. [PubMed: 17683874]
11. Kasukawa Y, Miyakoshi N, Mohan S: The anabolic effects of GH/IGF system on bone. *Curr Pharm Des* 2004, 10: 2577–2592. [PubMed: 15320746]
12. Samani AA, Yakar S, LeRoith D, Brodt P: The role of the IGF system in cancer growth and metastasis: overview and recent insights. *Endocr Rev* 2007, 28: 20–47. [PubMed: 16931767]
13. Khanna C, Prehn J, Hayden D, et al.: A randomized controlled trial of octreotide pamoate long-acting release and carboplatin versus carboplatin alone in dogs with naturally occurring osteosarcoma: evaluation of insulin-like growth factor suppression and chemotherapy. *Clin Cancer Res* 2002, 8: 2406–2412. [PubMed: 12114446]
14. Yakar S, Pennisi P, Wu Y, et al.: Clinical relevance of systemic and local IGF-I. *Endocr Dev* 2005, 9: 11–16. [PubMed: 15879684]
15. Baserga R: Targeting the IGF-1 receptor: from rags to riches. *Eur J Cancer* 2004, 40:2013–2015. [PubMed: 15341972] • A recent review summarizing important progress in the development of targeted anti-IGF-1 therapeutics.
16. Kolb EA, Gorlick R, Houghton PJ, et al.: Initial testing (stage 1) of a monoclonal antibody (SCH 717454) against the IGF-1 receptor by the pediatric preclinical testing program. *Pediatr Blood Cancer* 2008, 50:1190–1197. [PubMed: 18260118] • An example of the work produced by the Pediatric Preclinical Testing Program.
17. Phan TC, Xu J, Zheng MH: Interaction between osteoblast and osteoclast: impact in bone disease. *Histol Histopathol* 2004, 19:1325–1344. [PubMed: 15375775]
18. Dougall WC, Chaisson M: The RANK/RANKL/OPG triad in cancer-induced bone diseases. *Cancer Metastasis Rev* 2006, 25:541–549. [PubMed: 17180711]
19. Keller ET, Dai J, Escara-Wilke J, et al.: New trends in the treatment of bone metastasis. *J Cell Biochem* 2007, 102: 1095–1102. [PubMed: 17955492]
20. Yuasa T, Kimura S, Ashihara E, et al.: Zoledronic acid: a multiplicity of anti-cancer action. *Curr Med Chem* 2007, 14:2126–2135. [PubMed: 17691952]
21. Dass CR, Choong PF: Zoledronic acid inhibits osteosarcoma growth in an orthotopic model. *Mol Cancer Ther* 2007, 6(12 Pt 1): 3263–3270. [PubMed: 18089720]
22. Diel IJ, Fogelman I, Al-Nawas B, et al.: Pathophysiology, risk factors and management of bisphosphonate-associated osteonecrosis of the jaw: is there a diverse relationship of amino- and non-aminobisphosphonates? *Crit Rev Oncol Hematol* 2007, 64:198–207. [PubMed: 17855108]
23. Diel IJ, Solomayer EF, Costa SD, et al.: Reduction in new metastases in breast cancer with adjuvant clodronate treatment. *N Engl J Med* 1998, 339: 357–363. [PubMed: 9691101]
24. Bruland OS, Hoifodt H, Saeter G, et al.: Hematogenous micrometastases in osteosarcoma patients. *Clin Cancer Res* 2005, 11:4666–4673. [PubMed: 16000559]
25. Satija NK, Gurudutta GU, Sharma S, et al.: Mesenchymal stem cells: molecular targets for tissue engineering. *Stem Cells Dev* 2007, 16: 7–23. [PubMed: 17348802]
26. Shindo K, Kawashima N, Sakamoto K, et al.: Osteogenic differentiation of the mesenchymal progenitor cells, Kusa is suppressed by Notch signaling. *Exp Cell Res* 2003, 290: 370–380. [PubMed: 14567994]
27. Moss ML, Stoeck A, Yan W, Dempsey PJ: ADAM10 as a target for anti-cancer therapy. *Curr Pharm Biotechnol* 2008, 9: 2–8. [PubMed: 18289051]
28. Yan M, Plowman GD: Delta-like 4/Notch signaling and its therapeutic implications. *Clin Cancer Res* 2007, 13: 7243–7246. [PubMed: 18094402]
29. Eccles SA, Welch DR: Metastasis: recent discoveries and novel treatment strategies. *Lancet* 2007, 369: 1742–1757. [PubMed: 17512859]
30. Blattman JN, Greenberg PD: Cancer immunotherapy: a treatment for the masses. *Science* 2004, 305: 200–205. [PubMed: 15247469]

31. Meyers PA, Schwartz CL, Krailo M, et al.: Osteosarcoma: a randomized, prospective trial of the addition of ifosfamide and/or muramyl tripeptide to cisplatin, doxorubicin, and high-dose methotrexate. *J Clin Oncol* 2005, 23: 2004–2011. [PubMed: 15774791]
32. Meyers PA, Schwartz CL, Krailo M, et al.: Osteosarcoma: the addition of muramyl tripeptide to chemotherapy improves overall survival—a report from the Children’s Oncology Group. *J Clin Oncol* 2008, 26: 633–638. [PubMed: 18235123] • Update on recent phase 3 osteosarcoma clinical trial conducted in the United States.
33. Folkman J: Is angiogenesis an organizing principle in biology and medicine? *J Pediatr Surg* 2007, 42:1–11. [PubMed: 17208533]
34. DuBois S, Demetri G: Markers of angiogenesis and clinical features in patients with sarcoma. *Cancer* 2007, 109: 813–819. [PubMed: 17265525]
35. Ferrara N, Kerbel RS: Angiogenesis as a therapeutic target. *Nature* 2005, 438: 967–974. [PubMed: 16355214]
36. Maris JM, Courtright J, Houghton PJ, et al.: Initial testing of the VEGFR inhibitor AZD2171 by the pediatric preclinical testing program. *Pediatr Blood Cancer* 2008, 50: 581–587. [PubMed: 17457854]
37. Faivre S, Demetri G, Sargent W, Raymond E: Molecular basis for sunitinib efficacy and future clinical development. *Nat Rev Drug Discov* 2007, 6: 734–745. [PubMed: 17690708]
38. Rusk A, McKeegan E, Haviv F, et al.: Preclinical evaluation of antiangiogenic thrombospondin-1 peptide mimetics, ABT-526 and ABT-510, in companion dogs with naturally occurring cancers. *Clin Cancer Res* 2006, 12: 7444–7455. [PubMed: 17189418]
39. Birchmeier C, Birchmeier W, Gherardi E, Vande Woude GF: Met, metastasis, motility and more. *Nat Rev Mol Cell Biol* 2003, 4: 915–925. [PubMed: 14685170]
40. Scotlandi K, Baldini N, Oliviero M, et al.: Expression of Met/hepatocyte growth factor receptor gene and malignant behavior of musculoskeletal tumors. *Am J Pathol* 1996, 149: 1209–1219. [PubMed: 8863670]
41. Christensen JG, Burrows J, Salgia R: c-Met as a target for human cancer and characterization of inhibitors for therapeutic intervention. *Cancer Lett* 2005, 225: 1–26. [PubMed: 15922853]
42. MacEwen EG, Kutzke J, Carew J, et al.: c-Met tyrosine kinase receptor expression and function in human and canine osteosarcoma cells. *Clin Exp Metastasis* 2003, 20: 421–430. [PubMed: 14524531]
43. Corso S, Migliore C, Ghiso E, et al.: Silencing the MET oncogene leads to regression of experimental tumors and metastases. *Oncogene* 2008, 27: 684–693. [PubMed: 17684486]
44. Benvenuti S, Comoglio PM: The MET receptor tyrosine kinase in invasion and metastasis. *J Cell Physiol* 2007, 213:316–325. [PubMed: 17607709]
45. Chou A J, Gorlick R: Chemotherapy resistance in osteosarcoma: current challenges and future directions. *Expert Rev Anticancer Ther* 2006, 6: 1075–1085. [PubMed: 16831079]
46. Gu B, España L, Méndez O, et al.: Organ-selective chemoresistance in metastasis from human breast cancer cells: inhibition of apoptosis, genetic variability and microenvironment at the metastatic focus. *Carcinogenesis* 2004, 25: 2293–2301. [PubMed: 15347599]
47. Ory B, Moriceau G, Redini F, Heymann D: mTOR inhibitors (rapamycin and its derivatives) and nitrogen containing bisphosphonates: bifunctional compounds for the treatment of bone tumours. *Curr Med Chem* 2007, 14:1381–1387. [PubMed: 17584050]
48. Mita MM, Tolcher AW: The role of mTOR inhibitors for treatment of sarcomas. *Curr Oncol Rep* 2007, 9:316–322. [PubMed: 17588357]
49. Wan X, Mendoza A, Khanna C, Helman LJ: Rapamycin inhibits ezrin-mediated metastatic behavior in a murine model of osteosarcoma. *Cancer Res* 2005, 65: 2406–2411. [PubMed: 15781656]
50. Khanna C, Wan X, Bose S, et al.: The membrane-cytoskeleton linker ezrin is necessary for osteosarcoma metastasis. *Nat Med* 2004, 10: 182–186. [PubMed: 14704791]
51. Pearl LH, Prodromou C, Workman P: The Hsp90 molecular chaperone: an open and shut case for treatment. *Biochem J* 2008, 410: 439–453. [PubMed: 18290764]

52. Xu W, Neckers L: Targeting the molecular chaperone heat shock protein 90 provides a multifaceted effect on diverse cell signaling pathways of cancer cells. *Clin Cancer Res* 2007, 13: 1625–1629. [PubMed: 17363512]
53. Workman P, Burrows F, Neckers L, Rosen N: Drugging the cancer chaperone HSP90: combinatorial therapeutic exploitation of oncogene addiction and tumor stress. *Ann N Y Acad Sci* 2007, 1113: 202–216. [PubMed: 17513464]
54. Paoloni M, Khanna C: Translation of new cancer treatments from pet dogs to humans. *Nat Rev Cancer* 2008, 8: 147–156. [PubMed: 18202698] • Review of the comparative approach to cancer biology and therapy based on dogs that naturally develop cancer.
55. Mahajan A, Woo SY, Kornguth D G, et al.: Multimodality treatment of osteosarcoma: radiation in a high-risk cohort. *Pediatr Blood Cancer* 2008, 50: 976–982. [PubMed: 18213710]
56. Lalich M, McNeel D G, Wilding G, Liu G: Endothelin receptor antagonists in cancer therapy. *Cancer Invest* 2007, 25:785–94. [PubMed: 18058475]
57. Hughes DP, Thomas DG, Giordano TJ, et al.: Cell surface expression of epidermal growth factor receptor and Her-2 with nuclear expression of Her-4 in primary osteosarcoma. *Cancer Res* 2004, 64: 2047–2053. [PubMed: 15026342]
58. Chang HT, Chen WC, Chen JS, et al.: Effect of miconazole on intracellular Ca²⁺ levels and proliferation in human osteosarcoma cells. *Life Sci* 2005, 76: 2091–2101. [PubMed: 15826876]
59. Yao W, Zhuo J, Burns DM, et al.: Discovery of a potent, selective, and orally active human epidermal growth factor receptor-2 sheddase inhibitor for the treatment of cancer. *J Med Chem* 2007, 50: 603–606. [PubMed: 17256836]
60. Yang YA, Dukhanina O, Tang B, et al.: Lifetime exposure to a soluble TGF-beta antagonist protects mice against metastasis without adverse side effects. *J Clin Invest* 2002, 109: 1607–1615. [PubMed: 12070308]
61. Teicher BA: Transforming growth factor-beta and the immune response to malignant disease. *Clin Cancer Res* 2007, 13:6247–251. [PubMed: 17975134]
62. Shor AC, Keschman EA, Lee FY, et al.: Dasatinib inhibits migration and invasion in diverse human sarcoma cell lines and induces apoptosis in bone sarcoma cells dependent on SRC kinase for survival. *Cancer Res* 2007, 67: 2800–2808. [PubMed: 17363602]
63. Kim SY, Lee CH, Midura BV, et al.: Inhibition of the CXCR4/CXCL12 chemokine pathway reduces the development of murine pulmonary metastases. *Clin Exp Metastasis* 2008, 25:201–211. [PubMed: 18071913]
64. Roberts WG, Ung E, Whalen P, et al.: Antitumor activity and pharmacology of a selective focal adhesion kinase inhibitor, PF-562,271. *Cancer Res* 2008, 68:1935–1944. [PubMed: 18339875]
65. Bagatell R, Beliakoff J, David CL, et al.: Hsp90 inhibitors deplete key anti-apoptotic proteins in pediatric solid tumor cells and demonstrate synergistic anticancer activity with cisplatin. *Int J Cancer* 2005, 113:179–188. [PubMed: 15455381]
66. Gordon EM, Lopez FF, Cornelio GH, et al.: Pathotropic nanoparticles for cancer gene therapy Rexin-G IV: three-year clinical experience. *Int J Oncol* 2006, 29: 1053–1064. [PubMed: 17016635]
67. Cunningham CC: Talabostat. *Expert Opin Investig Drugs* 2007, 16:1459–1465.
68. Steinert DM, Patel SR: Recent studies in novel therapy for metastatic sarcomas. *Hematol Oncol Clin North Am* 2005, 19:573–590, viii. [PubMed: 15939198]
69. Salmon BA, Siemann DW: Characterizing the tumor response to treatment with combretastatin A4 phosphate. *Int J Radiat Oncol Biol Phys* 2007, 68:211–217. [PubMed: 17448875]

Table 1.

Novel osteosarcoma targets and therapeutics

Study	Target	Therapeutic agent/class	Target credentials*	Agent example	Development status
Bone targets					
Baserga [15••]	IGF-1 receptor	Antibody, kinase inhibitor	III	Many	Clinical (phase 2) [‡]
Keller et al. [19]	RANK	Bisphosphonate	III	Pamidronate, zoledronate	Preclinical/clinical
Mahajan et al. [55]	Osteoblast/bone	Bone-seeking radionuclide	III	Samarium-153	Preclinical/clinical
Lalich et al. [56]	Endothelin receptor	Receptor antagonist	II	Atrasentan	Concept/preclinical
Hughes et al. [57]	ErbB2	Antibody, kinase inhibitor	II	Trastuzumab	Clinical
Chang et al. [58]	Endoplasmic reticulum calcium flux	Enzyme inhibition	II	Miconazole	Concept/preclinical
Yao et al. [59]	Notch	Sheddase inhibitor	I	INCB3619	Concept/preclinical
Yang et al. [60], Teicher [61]	TGF- β /TGF- β receptor	Antibody, kinase inhibitor	I	GC1008	Concept/preclinical
Metastatic process targets					
Maris et al. [36]	VEGF receptor (angiogenesis)	Antibody, kinase inhibitor	III	Many	preclinical/clinical [‡]
Shor et al. [62]	Src kinase (invasion)	Kinase inhibitor	III	Dasatinib, AZD0530	preclinical/clinical [§]
Meyers et al. [32•]	Immune activation	Macrophage activator	III	MTP-PE	Clinical
MacEwen et al. [42]	c-Met (motility, migration, survival)	Kinase inhibitor	III	XL880	Preclinical
Kim et al. [63]	CXCR4 (adherence/survival)	Competitive peptide inhibitor	III	CTCE-9908	Preclinical
Roberts et al. [64]	FAK (adherence/migration)	Kinase inhibitor	I	PF-562271	Concept/preclinical
Metastatic lesion targets					
Mita and Toleher [48]	Mammalian target of rapamycin	Competitive or kinase inhibitor	III	Rapamycin, rapalogues	Preclinical/clinical [¶]
Bagatell et al. [65]	Heat shock protein 90	Competitive inhibitor	III	17-AAG	Preclinical/clinical
Gordon et al. [66]	Cyclin G1	Mutant pathotropic retrovirus	III	Rexin-G (Epeius, San Marino, CA)	Preclinical/clinical
Cunningham [67]	Fibroblast activation protein	Dipeptidyl peptidase inhibitor	III	Talabostat	Preclinical/clinical
Steinert and Patel [68]	Proteosome	Proteosome inhibitor	I	Bortezomib	Preclinical/clinical
Salmon and Siemann [69]	Vasculature/endothelial cell	Vascular-disrupting agent	I	Combrestatin	Concept/preclinical

*Target credentials: I—validated in other cancer only; II—expressed or overexpressed in osteosarcoma; III—inhibition of target induces desirable anticancer phenotype in osteosarcoma.

[‡]May have overlap with metastatic process and metastatic lesions.

[§]May have overlap with metastatic lesions.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

[§]May have overlap with bone targets.

[¶]May have overlap with bone targets and metastatic process.

IGF—insulin-like growth factor; MTP-PE—muramyl tripeptide phosphatidyl ethanolamine; RANK—receptor activator for nuclear factor κ -B; TGF—transforming growth factor; VEGF—vascular endothelial growth factor.