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Stratifying Osteosarcoma: Minimizing and Maximizing Therapy

Lisa M. Niswander, Su Young Kim

Pediatric Oncology Branch, National Cancer Institute, National Institutes of Health, 10 Center Drive, Building 10, CRC 1w-3750, Bethesda, MD 20892, USA

Abstract

Patients who are newly diagnosed with osteosarcoma face a daunting year of medical and surgical therapy, often filled with hospitalizations and changes in lifestyle. Fortunately, the majority of patients endure this struggle to become long-term survivors. However, follow-up studies of cancer survivors are revealing the sequelae of this curative therapy. Just as disturbingly, there remains a large subset of patients for whom conventional therapy is inadequate and who succumb to disease. In this review, we propose that therapeutic strategies for osteosarcoma patients must rely on stratification of patients into risk categories, in order to minimize therapy for some, while expanding treatment for others. We then focus on two molecular targets for the treatment of patients with high-risk osteosarcoma.

Keywords

Osteosarcoma; Risk stratification; Targeted therapy

Introduction

Osteosarcoma is the most common pediatric bone malignancy in the United States [1]. Fifty years ago, surgery was the only available treatment, and survival was abysmal at less than 20% [2]. Treatment of patients with osteosarcoma was transformed in the 1980 s and 1990 s with advances in chemotherapy and orthopedic surgical techniques, leading to long-term survival rates that now approach 70% [3]. Unfortunately, further improvement in survival has not occurred in the last decade despite multiple attempts at intensification of chemotherapy and trials utilizing new agents. These data suggest many interesting facets about the natural history and biology of osteosarcoma that can guide us in our therapeutic approaches. First, there is a small cohort of patients who are cured with surgery alone. Second, about half of the patients are currently receiving an appropriate level of treatment. Lastly, a sizeable number of patients require novel and alternative approaches if they are to have any chance for long-term survival. Our premise is that we need to stratify patients into low-risk, average-risk, and high-risk groups, thus setting the framework for modulated therapy in order to minimize morbidity and improve mortality rates. In this review, we

S. Y. Kim, kimsuyou@mail.nih.gov.

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briefly discuss the prospects of identifying low-risk patients, followed by a discussion of novel targeted-therapy approaches for high-risk patients.

Low-Risk Osteosarcoma

The vast majority of osteosarcoma originates in the metaphysis of long bones, and before the 1980 s treatment involved amputation of the affected extremity when possible [3]. Despite this radical surgical approach, survival was dismal and approximately 80% of patients, who appeared to have localized disease, developed lung metastases within 5 years [2, 4, 5]. This clinical course implies that a large number of patients with osteosarcoma have micrometastatic disease. Further strengthening this hypothesis is the fact that the addition of chemotherapy resulted in a dramatic improvement in survival, suggesting that surgery is necessary to control the primary tumor and chemotherapy is needed to eliminate metastatic disease.

The data above also demonstrate that surgery alone is curative for approximately 15% of patients, thus defining a low-risk osteosarcoma subgroup. A follow-up study performed at the Mayo Clinic verified that 83 of the 465 patients (18%) that they observed with high-grade osteosarcoma of the extremity who received surgery only remained free of disease for a 10-year period [4]. Although the percentage of truly low-risk patients is small, they comprise a distinct cohort for whom chemotherapy and the concomitant toxicities associated with these regimens are unnecessary. Unfortunately, we have not been able to determine which patients make up this low-risk cohort. It would be unethical to design a clinical study withholding chemotherapy from patients with localized disease when 70% are cured with multimodal treatment. Therefore, researchers and clinicians must devise innovative ways to identify these patients.

One possible solution is to utilize the biological similarities of dogs with osteosarcoma as a model to define the low-risk human population. The parallels between human and spontaneous canine osteosarcoma have been well described [6, 7]. Dogs develop tumors in their extremities and many eventually die due to metastatic lung disease if treated with surgery alone. Microarray studies have shown that tumor samples from dogs and humans share many components. These findings suggest that the natural history and biology between these two populations have many similar qualities [8]. The major differences are that canine tumors most commonly involve the forelimbs and that many more dogs are affected, with an incidence that is tenfold greater than in humans [6]. The latter is a very important and useful feature, as many more tumor samples can be collected in a shorter period of time for dogs. Another advantage in this comparative oncology model is the difference in lifespan. One-year survival in dogs is comparable to 5-year survival in humans, allowing clinical trials to be performed in a much shorter period of time.

Recently, the Comparative Oncology Program at the National Cancer Institute began collecting tumor samples in a large outcome-linked bio-specimen repository [9]. Many pet owners elect to forgo chemotherapy for their dogs and opt for treatment with surgical resection alone. Because of this, the majority of the samples in the repository will be chemo-naïve, unlike most human tumor samples that are available for study. In 1 to 2 years, as the

repository continues to grow, it will be possible to stratify dogs into chemo-naïve animals who died of disease, versus those who survived long-term. Using gene expression or proteomic analysis, we could then try to determine a “low-risk” signature for the dogs that survived with surgery alone. We could utilize this signature to determine which dogs would survive long-term in the absence of chemotherapy in a prospective study. This “low-risk” signature could then be assessed retrospectively in humans. If successful, this would then set the stage for a prospective study of treatment with surgery alone for patients in the low-risk cohort, thus sparing them the unnecessary morbidities associated with chemotherapy.

High-Risk Osteosarcoma

Unfortunately, our current treatment regimens are not sufficient to cure the 30% to 35% of patients who we classify as “high risk.” This group of patients includes those who present with metastatic disease (20% survival rate), patients with incomplete surgical resection (15% survival rate), and those with disease recurrence, especially those who are not amenable to subsequent surgical resection (< 20% survival rate) [3, 10, 11]. Despite the immense benefit of chemotherapy to the overall survival of osteosarcoma patients, the numbers above demonstrate that current therapeutic regimens are insufficient for these patients. Even more disappointingly, over the years, we have done little to improve outcomes for patients in this cohort despite multiple attempts at dose intensification and alternative treatments [12]. This high-risk group is in need of new therapeutic strategies.

There has been much interest in investigating molecular targets for therapy in osteosarcoma. These myriad targets include HER2/neu, IGF-1R, PDGFR, Notch, c-MET, Hsp90, RANKL, CXCR4, mTOR, as well as many others, and have been extensively reviewed previously [13, 14]. Because so many others have discussed these considerations, in this review we will focus our attention on the rationale, biology, and drug development of two promising targets in osteosarcoma: vascular endothelial growth factor (VEGF) and the integrin family.

Promising Targets for Osteosarcoma Therapy

VEGF

Angiogenesis is widely accepted as an essential step in malignant tumor progression and metastasis [15]. Tumors are thought to acquire an angiogenic propensity by local expression of proangiogenic factors including basic fibroblastic growth factor, platelet-derived growth factor, and VEGF [16]. VEGF-A, and its receptors VEGFR-1 and VEGFR-2, in association with other proangiogenic factors, can aid in the mobilization of endothelial cell precursors from bone marrow and stimulate their proliferation, migration, and incorporation into the assembly of new vessels [17]. Expression of VEGF in primary osteosarcoma samples is correlated with the development of pulmonary metastases and poor prognosis [18, 19]. In addition, blockade of the VEGF cascade with retroviral transduction of soluble decoy VEGF receptor slows the growth of osteosarcoma cells in vivo [20].

Bevacizumab, a humanized monoclonal anti-VEGF antibody, has been approved by the US Food and Drug Administration for the treatment of metastatic colon cancer, non-small-cell lung cancer, metastatic HER2-negative breast cancer, metastatic renal cell carcinoma, and

glioblastoma. The success of bevacizumab in targeting angiogenesis via VEGF encouraged the generation of new antiangiogenic therapies, several of which are currently being tested in clinical trials. Despite positive results in adult malignancies, clinical experience with bevacizumab in the pediatric population has been limited.

Recently, bevacizumab was assessed on a compassionate-use basis in 15 heavily pretreated children and young adults with recurrent or refractory solid tumors [21]. Bevacizumab was well tolerated in these patients, and some antitumor activity was noted, although this cohort did not specifically include any patients with osteosarcoma. A Children's Oncology Group phase 1 study of bevacizumab alone in pediatric patients with refractory solid tumors also found that the treatment was well tolerated with no dose-limiting toxicities [22]. The phase 1 experience of bevacizumab in pediatric patients, and the preclinical data demonstrating the role of VEGF in osteosarcoma, prompted a clinical trial of bevacizumab in combination with standard chemotherapy for treatment of patients with osteosarcoma (NCT00667342). This trial has two primary objectives: to study the feasibility of combining bevacizumab with first-line chemotherapy in all patients with newly diagnosed osteosarcoma and to study the effect of adding bevacizumab to chemotherapy on the event-free survival of patients with localized and resectable osteosarcoma compared to historical controls.

Another agent that targets angiogenesis and is potentially applicable to osteosarcoma is cediranib (AZD2171), an orally bioavailable tyrosine kinase inhibitor of multiple members of the VEGFR family [23]. Cediranib, either as monotherapy or in combination with chemotherapy, has resulted in some partial responses and stable disease in phase 2/3 trials in lung, breast, prostate, renal, ovarian, and colorectal cancers [24]. The Pediatric Preclinical Testing Program assessed cediranib on in vitro and in vivo tumor panels and observed in vivo antitumor activity in 4 of 5 osteosarcoma tumor xenografts, including two with progressive disease after a growth delay, one with stable disease, and one complete response [25]. Other preclinical studies have suggested increased antitumor activity with the combination of cediranib and inhibition of epidermal growth factor receptor (EGFR) [26, 27]. These findings were translated into a recently published phase 1 evaluation of the safety and tolerability of cediranib in combination with gefitinib, an EGFR tyrosine kinase inhibitor, in patients with advanced tumors. Eight of 90 patients (9%) had a confirmed partial response, including one patient with osteosarcoma, and 38 patients (42%) had stable disease [28]. These results suggest a potential role for dual therapy with cediranib and gefitinib in the targeted treatment of osteosarcoma.

Integrins

Integrins are a 24-member family of heterodimeric transmembrane proteins containing two subunits, α and β , in different combinations of 18 α and 8 β subunits [29]. Through association with the surrounding extracellular matrix, integrins transmit cues from the cellular microenvironment to intracellular signaling pathways, thus orchestrating cellular processes that are focal to tumor biology such as cell adhesion, survival, migration, and invasion [30]. A wide variety of integrins have been implicated in poor prognosis or progression of breast, prostate, pancreatic, ovarian, cervical, colon, and non-small cell lung carcinomas, as well as glioblastoma [31]. Therefore, there has been much interest in

developing targeted integrin inhibitors for cancer therapy. To date, the most promising inhibitor is cilenglitide, which antagonizes proangiogenic integrins $\alpha v\beta 3$ and $\alpha v\beta 5$. It is currently in phase 2 trials for lung and prostate cancer and in a phase 3 trial with radiation therapy and temozolomide for glioblastoma (NCT00689221 [31•]). This is the first phase 3 oncology trial for integrin-targeted therapy. There are several other agents that inhibit members of the integrin family in preclinical and clinical trials, such as CNTO 95, volociximab, and ATN-161 [31•].

Integrin $\alpha 6\beta 4$ is structurally distinct from other integrin family members due to an atypically lengthened $\beta 4$ cytoplasmic domain. The contribution of $\alpha 6\beta 4$ to carcinoma progression through synergy with growth factor receptors and activation of the PI3-K pathway has been well characterized [32]. The cooperation of $\alpha 6\beta 4$ with oncogenic receptors in tumorigenesis is illustrated by the interaction of this integrin with ErbB2 and ErbB3 of the EGFR family in breast carcinoma development [33, 34]. Clinical and in vivo experimental studies in several carcinomas have described an association between overexpression of $\alpha 6\beta 4$ and metastasis [35].

While the contribution of many members of the integrin family to carcinoma pathogenesis has been well established, there has not been much focus on the role of integrins in sarcomas. However, a recent publication demonstrates that $\alpha 6\beta 4$ integrin is highly expressed in osteosarcoma cell lines and 94% (45/48) of assayed tumor samples [36]. In addition, knockdown of $\beta 4$ expression using shRNA constructs and interference using a dominant negative $\beta 4$ clone both inhibited the metastatic capability of high $\alpha 6\beta 4$ -expressing MNNG-HOS osteosarcoma cells in several in vivo mouse experiments. These data suggest that integrin $\beta 4$ is crucial to the metastasis of MNNG-HOS osteosarcoma cells. Taken in the context of our current paucity of effective therapies for metastatic disease, the finding of $\beta 4$ integrin overexpression in the majority of human osteosarcoma samples implies a potentially wide-reaching benefit for targeting of integrins in osteosarcoma and awaits the development of specific therapeutic agents.

Conclusions

In the last 20 years, there have not been any dramatic improvements in therapy for patients with osteosarcoma. Multiple attempts at intensification of current regimens or trials using different agents have had only limited success, demonstrating the need for novel approaches. Two specific areas that are in need of further research efforts were described above. First, we require a way to stratify patients into risk groups. To this end, researchers and clinicians must develop innovative ideas on how to identify low-risk patients who can be cured with surgery alone, thus minimizing both short-term and long-term toxicities. Second, patients who are at high risk of failing with current conventional therapy desperately require additional strategies. Continued research will allow for further advances in the identification of molecular targets that are amenable to pharmaceutical intervention, specifically for patients with high-risk osteosarcoma.

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