Osteosarcoma therapy: what is the way forward?

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At the start of the twentieth century, the prognosis of osteosarcoma, the most common primary bone sarcoma, was grim, with a 5-year overall survival rate of only ~20% in the year 1910, with little change over the next 50 years. However, beginning in the 1960s, the situation began to improve, thanks to surgical approaches combined with polychemotherapy, and by the 1980s the survival rate reached about 60%. Unfortunately, since then, the survival rate has leveled off. ‘After 30 years of lack of progress,’ wrote the authors of a recent meta-analysis of osteosarcoma outcomes, ‘we should re-evaluate our treatment paradigms and think along different lines, especially in regard to the current players behind drug and medical technology development, as well as our own attitudes toward disease treatment and outcomes we deem appropriate.’

In Recent Advances in the Therapy of Osteosarcoma, a recent IBMS BoneKey webinar, presenter Bruno Fuchs (University of Zurich, Switzerland) and a distinguished panel outlined key components of a research agenda that may make further improvements in the clinic possible. Key to that agenda, they said, will be a better understanding of the biology of osteosarcomas made feasible by an increased number of preclinical studies. For any new drug candidate, ‘we have to establish a very strong basis through in vitro and in vivo analysis before bringing that drug into patients,’ Dr Fuchs said. The message of the webinar was that with a better grasp of osteosarcoma biology gained through well-organized international research efforts, along with better orchestrated efforts on the clinical side, investigators have reason to be hopeful for the future treatment of these rare tumors.

Panelists for Recent Advances in the Therapy of Osteosarcoma included Anne-Marie Cleton-Jansen (Leiden University Medical Center, The Netherlands) and Fernando Lecanda (University of Navarra, Spain). The panel discussion was moderated by Dominique Heymann (INSERM, University of Nantes, France).

The webinar is available on the BoneKey Knowledge Environment at: http://www.nature.com/bonekey/webinars/index.html?key=webinar26.

The Present

Dr Fuchs began his presentation with a discussion of current approaches used to manage osteosarcoma, including surgical treatment. Ten percent of osteosarcoma patients require amputation, but for those with a pathological fracture, Dr Fuchs noted that a recent meta-analysis supports the use of limb salvage as a surgical alternative to amputation.2 Limb salvage surgery, which aims to remove cancerous cells while maintaining limb function, is benefitting from image-guided computer navigation that helps the surgeon delineate tumors and from the use of hand-held imaging devices that help detect and remove microscopic residual sarcoma cells in the intraoperative setting.3,4

Although the need for amputation is now the exception rather than the rule in osteosarcoma patients, Dr Fuchs said that surgical progress in limb reconstruction has stalled, pointing to a 2011 review article that concluded that ‘no really new ideas have been brought forward for at least a decade’.5 Dr Fuchs said that new surgical techniques or approaches are unlikely; any advances will be incremental ones that will hopefully reduce complications, such as infection.

Progress in managing local recurrence of osteosarcoma has also faltered, Dr Fuchs said. Recurrence rates have remained steady, between 10 and 20%, since the 1970s.1

In terms of pharmacological approaches, chemotherapeutic drugs, including doxorubicin, cisplatin, ifosfamide and high-dose methotrexate have been used for decades in osteosarcoma treatment. Chemotherapies are being tested in the European and American Osteosarcoma Study (EURAMOS) Group 1 clinical trial, the largest osteosarcoma trial ever, with >2500 patients at centers in the United States and Europe.

However, chemotherapy for osteosarcoma patients with metastatic disease has been of limited benefit, as 5-year survival rates for such individuals have remained the same since the 1970s.1 Although preclinical work has identified many molecular alterations characteristic of the different steps of metastasis,6 which of those changes will serve as the best therapeutic target remains uncertain. ‘We have still not found the Holy Grail to this day,’ Dr Fuchs said.

The Challenge

Why has it been so difficult to make progress on treating osteosarcoma? One of the key obstacles is that these tumors are a highly varied lot. A number of different histological subtypes have already been identified, and Dr Fuchs noted that additional subtypes are likely to be characterized in the future. Furthermore, many complicated signaling pathways have been
implicated in osteosarcomas. ‘The biology of osteosarcomas is extremely heterogeneous, and this of course makes testing and defining new drugs extremely difficult,’ he said.

One way in which osteosarcomas vary is in their tendency to spread to other tissues, with some tumors showing extremely metastatic behavior from the outset, whereas others are more indolent. Although autonomous mechanisms intrinsic to osteosarcomas play a large role in determining the metastatic activity of these tumors, interactions between osteosarcoma cells and other cells within the bone microenvironment are also critical, said panelist Fernando Lecanda. ‘There is crosstalk with a variety of different types of cells within the bone microenvironment that is going to change the behavior of the tumor. These interactions are poorly understood,’ he said. Interactions between tumor cells and stromal cells, endothelial cells and macrophages are particularly important.

Once osteosarcoma cells leave the bone microenvironment and enter the bloodstream, they have a strong tendency to metastasize to the lungs, where interactions between the tumor cells and epithelial cells become especially important, Dr Lecanda said. And throughout the entire process of metastasis from the bone to the lungs, patterns of gene expression change: at first, in the bone, initiation genes are activated that are important for tumorigenesis and the maintenance of the tumors. But then, once the tumor cells escape to the circulation, genes that allow the cells to survive in the blood are activated. Once in the lungs, certain genes are deactivated, likely through interactions between the tumor cells and epithelial cells, Dr Lecanda explained.

Genes involved with the activity of macrophages seem to have a crucial role in osteosarcoma metastasis, said panelist Anne-Marie Cleton-Jansen. She described results of a gene profiling study she and her colleagues performed using prechemotherapy biopsies from osteosarcoma patients with and without metastases. They found that half of the genes upregulated in patients with metastases were related to macrophage function. Further analysis of the tumors also suggested a role for macrophages. ‘We found that macrophages are actually enriched in tumors that do not metastasize,’ she said. ‘It appears that the macrophages protect the tumor cells from further spreading.’

The involvement of macrophages in metastasis, Dr Cleton-Jansen said, could explain the beneficial effects of muramyl tripeptide (MTP), a synthetic analog of a bacterial cell wall component that can activate macrophages, in osteosarcoma; MTP is one of the very few agents that represent an advance component that can activate macrophages, in osteosarcoma; and when added to chemotherapy, improved 6-year overall survival of osteosarcoma patients from 70 to 78% ($P = 0.03$; relative risk $= 0.71$),

The Future

Despite the complex biology of osteosarcoma, including the multifaceted cellular crosstalk and genetic programs characteristic of the disease, the webinar highlighted many reasons to be optimistic about the future treatment of this tumor. For instance, in addition to MTP treatment, other immunomodulatory approaches have promise. For instance, investigators are intrigued about using interferons to treat osteosarcoma, and those agents were tested as adjuvant therapy in EURAMOS 1; investigators are eagerly anticipating the results. Another immunomodulatory approach that has been tried in osteosarcoma is the use of granulocyte macrophage colony-stimulating factor (GM-CSF). Unfortunately, a feasibility study of inhaled GM-CSF in patients with pulmonary recurrence of osteosarcoma found no immunomodulatory effect on osteosarcoma in lung nodules. Nonetheless, an inhaled route of administration is a new strategy to treat lung metastases directly, according to Dr Fuchs, who noted that three clinical trials using an inhaled route of administration to treat pulmonary metastases are underway, including one trial using inhaled GM-CSF and two using inhaled liposomal cisplatin.

Other emerging therapeutic targets in osteosarcoma, which were the focus of the second half of Dr Fuchs’ presentation, are the intracellular signaling pathways implicated in the disease, and a number of clinical trials of agents that interfere with those pathways are underway. For instance, the Src kinase inhibitor AZD0530 (saracatinib) is being tested in patients with recurrent osteosarcoma localized to the lung, although a 2009 study found that while inhibiting Src phosphorylation inhibited the adhesion and migration of osteosarcoma cells in vitro, it had no effects on the development of pulmonary metastases in vivo. Mammalian target of rapamycin (mTOR) signaling is another intracellular pathway of interest to osteosarcoma researchers. A phase 2 study published last year tested ridaforolimus, an inhibitor of the mTOR pathway, in patients with advanced bone and soft tissue sarcomas. That study found that progression-free survival in patients treated with ridaforolimus was similar to that seen in trials of other agents used in sarcoma patients, and based on that result, a phase 3 trial of ridaforolimus is underway.

Tyrosine kinase receptors are another type of emerging target that has also seen a great deal of attention in osteosarcoma studies. For instance, clinical trials have tested trastuzumab to target human epidermal growth factor receptor 2 (HER-2), cixutumumab to target the insulin-like growth factor I receptor (IGF-IR), sorafenib to target vascular endothelial growth factor (VEGF) receptors, and the multikinase inhibitor, OSI-930, to target vascular endothelial growth factor receptors, c-Kit and platelet-derived growth factor receptors. Interest remains in all of these approaches, Dr Fuchs said. There has also been interest in another strategy, the use of pemetrexed, which is an antifolate that inhibits folate-dependent enzymes that have a role in nucleotide biosynthesis, although a recent phase 2 trial found that the agent did not have antitumor activity, despite evidence of such activity in in vitro studies.

Another area of opportunity to improve osteosarcoma treatment is to focus on a key cell in the bone microenvironment, the osteoclast, and Dr Fuchs mentioned evidence from recent studies giving reason for optimism. For instance, in an open-label, phase 2 study of the receptor activator of nuclear factor-κB ligand (RANKL) inhibitor, denosumab, in patients with giant-cell tumor of bone, 30 of 35 patients showed a tumor response as assessed by histology or by radiology. Also, a recent JBMR study found that, in rodent models of osteosarcoma, small-interfering RNAs targeting RANKL prevented osteolysis and enhanced tumor responses to the chemotherapeutic agent ifosfamide. Bisphosphonates could also have utility in the osteosarcoma setting. For example, a 2011 safety and feasibility study in 40 patients with osteosarcoma found that adding pamidronate to cisplatin, doxorubicin and methotrexate chemotherapy did not impair the
efficacy of chemotherapy,20 and Dr Fuchs pointed to clinical trials of zoledronic acid that are ongoing to further test bisphosphonates in the osteosarcoma setting. Potential pro-apoptotic effects of bisphosphonates on tumor cells, Dr Lecanda noted, also make those agents an attractive treatment for osteosarcoma. Finally, moderator Dominique Heymann referred to recent work by David Roodman et al.,21 suggesting that osteoclasts can stimulate angiogenesis, which provides yet another reason to target bone-resorbing cells with anti-resorptive agents in osteosarcoma.

While work will continue on the clinical side, there are also opportunities for new preclinical studies that could shed much-needed light on osteosarcoma biology. Osteosarcoma has been difficult to study, Dr Cleton-Jansen said, because it is a rare tumor for which it is difficult to obtain material, as well as a heterogeneous and genetically unstable tumor. However, there are now many tools available, she said, including animal models of the disease. For instance, she described a zebrafish embryo model she and her colleagues are using to study angiogenesis in osteosarcoma, having found in that model that tumorigenic transformed mesenchymal stem cells induce angiogenesis.22

‘I think that we can be optimistic for the future,’ Dr Heymann said to conclude the webinar. ‘The future of osteosarcoma therapy will likely be based on a multidisciplinary approach,’ he emphasized, including direct targeting of cancer cells, along with targeting of the bone microenvironment and perhaps even of tumor stem cells, while the assessment and treatment of metastasis could be aided by the detection of circulating tumor cells.

Conflict of Interest

The author declares no conflict of interest.

References

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