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Perspective Article

Summary – Osteosarcoma session

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Insights into rare cancers have repeatedly led to discoveries relevant to more common cancers and normal cell biology. In bone research, non-metastatic osteosarcoma cell lines provided the first insights into osteoblast biology, but relatively little insight into the oncogenesis of osteosarcoma. **Dr. R. Gorlick** provided a comprehensive overview of the current state-of-the-art, recent clinical trials, and the challenges faced by clinicians treating osteosarcoma. While there were breakthroughs in clinical care regimens to include neo-adjuvant and adjuvant therapy and limb sparing surgery that resulted in a drop in mortality from 90% to 30% in the 1970s, there has been little new progress since then. Unlike most other cancers, there are no reliable tests to evaluate probability of sarcoma progression, metastases, and death, apart from evaluating the extent of tumor necrosis after chemotherapy. There are many new cancer drugs being developed. Animal models and clinical protocols that would guide decisions on their usefulness for treatment of osteosarcoma in young people are needed. The dilemma remains that because of the relatively few cases of osteosarcoma, there are not enough clinical subjects to test all the promising compounds. The most recent collaborative US clinical trial testing of a new combination of chemotherapeutic drugs showed no advantage over existing therapy, leaving unclear the next steps to develop improved therapies.

Interest in the increased risk of osteosarcoma following exposure to bone-seeking radionuclides has increased recently with the nuclear power plant accidents in Russia and the intent to use plutonium in warfare. **Dr. S. Miller** has had unique opportunities to visit Russian locations exposed to high levels of bone-seeking radionuclides and to work with an international team evaluating risks to human health. Surprisingly, while the risk for all tumors is increased, the risk of osteosarcoma, even in the face of excessive plutonium exposure, was less than anticipated. Unlike sporadic osteosarcoma, the long-term dog studies at the University of Utah have shown a bone pre-lesion as excessive fibrosis adjacent to bone and a predilection for hematopoietic bone sites within trabecular bone. The pre-lesion is more commonly associated with volume-seeking radionuclides such as radium, rather than with surface seeking radionuclides, such as plutonium. There is very little work determining whether sarcomagenesis of radiation-induced osteosarcoma and sarcomagenesis of spontaneous osteosarcoma share any common pathogenesis, or whether they arise from perturbations in distinctly different signaling pathways.

The genetics of human osteosarcoma show multiple chromosomes and genes are involved in sarcomagenesis in bone. New animal models and *in vitro* tests need to be developed as the single gene induction of osteosarcoma seen in mice with genetically modified expression of c-fos, v-myc, Nf2 and SV40 large T antigen do not mimic the human disease other than in the end outcome. The newest hypothesis, presented by **Dr. M. Hansen's** group at the University of Connecticut and based on examination of genetic abnormalities in human osteosarcoma, suggests that mutations in a 3rd cell cycle controller, in addition to the known association with mutant or missing p53 and Rb, is present in human osteosarcoma. It remains unclear whether these changes in cell cycle occur in the development of lesions or lie at the heart of its etiology. In addition, evidence is mounting that the RANK/RANKL/OPG signal transduction pathway is significantly impaired in osteosarcoma. It is not known whether this impairment is a localized event exclusive to osteosarcoma, or a more general perturbation in the host. More attention needs to be paid to the multiple new genes being identified through microarrays and other differential gene expression technologies. Their relevance both to impaired osteoprogenitors and osteoblast functions in osteosarcoma as well as potential key roles in normal osteoblast and bone biology needs to be considered.

Bone cancer pain has not been systematically evaluated and understood by the bone research community. **Dr. P. Mantyh** and his group from the University of Minnesota presented innovative work on new mouse xenograft models they have created to investigate bone cancer pain of metastases from soft tissue tumors elsewhere and from primary lytic osteosarcoma cells. They have established a comprehensive set of criteria to evaluate pain in long bones, which would be relevant to many other avenues of bone biology. Inhibition of osteo-

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clasts by selective COX2 inhibitors or bisphosphonates uncovered a key role for osteoclasts in bone pain, associated with the impact of bone resorption on the physical location of the sensory innervation on bone surfaces. There was considerable debate on why some chronic human diseases in which bone resorption played a key role in pathogenesis were not associated with intractable bone pain. To better understand these discrepancies, improved communication between neurobiologists and bone biologists is needed. As a research community, we need to develop a much greater awareness of pain and the means to evaluate and treat it in our research on bone diseases and their animal models.