

ADVANCES IN ONCOLOGY

Current Developments in the Management of Solid Tumor Malignancies

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Skeletal-Related Events in Prostate Cancer



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H&O How do skeletal-related events manifest in men with prostate cancer?

MS In men with prostate cancer, bone is the dominant, and often the only, site of metastatic disease. Skeletal complications related to bone metastases are a dominant part of the clinical condition. Most men with fatal prostate cancer die either with or from complications of bone metastases. Bone metastases result in marked alterations in bone metabolism and impair the biomechanical integrity of bone, often leading to microfractures and poor hematopoiesis. There is also a risk that metastases will entrap nerves adjacent to the bone. Bone metastases may also encroach on the bone marrow space where new blood cells are made.

Most of these complications involve pain, due to expansion of the bone metastasis or fractures that occur because of impaired biomechanical integrity of bone. Patients with progressive skeletal pain may require further systemic treatment, such as chemotherapy, or radiation to specific sites. Patients with generalized, diffuse bone pain may need treatment with radiopharmaceuticals. Another complication of bone metastasis is spinal cord compression caused by local extension of the tumor that compresses the spinal cord. This condition is uniformly painful and associated with neurologic compromise. It is one of the most devastating skeletal complications and can result in loss of mobility.

H&O Which men would benefit from preventive care of skeletal-related events?

MS Most men with metastatic prostate cancer are at risk for skeletal complications. The greatest need for prevention is in men whose underlying malignancy is poorly controlled.

Accordingly, studies on the prevention of skeletal complications have focused on men with castration-resistant disease, meaning disease that progresses despite standard androgen-deprivation therapy. In recent years, there has been meaningful progress in the management of castration-resistant disease, although many challenges remain.

H&O What are the options for prevention of bone metastases in these men?

MS Zoledronic acid (Zometa, Novartis) is the only bisphosphonate shown to be effective for reducing skeletal-related events. In 2002, zoledronic acid was the first drug approved for prevention of skeletal-related events, based on a placebo-controlled trial. It has been shown to be effective in other diseases as well, but it is specifically approved in prostate cancer. It is given intravenously monthly. The main adverse events are acute-phase reaction and bone pain. More serious adverse events include renal failure and osteonecrosis of the jaw.

Denosumab (Xgeva, Amgen) is a targeted therapy. It binds and inactivates the RANK ligand (RANKL), a key pathway involved in osteoclast formation, function, and survival. Denosumab is a more potent inhibitor of osteoclast than is zoledronic acid. In a large, international, head-to-head study, denosumab was shown to be superior to zoledronic acid for the prevention of skeletal-related events in men with castration-resistant metastatic prostate cancer. It has been approved for prevention of skeletal-related events in the United States and many other parts of the world. Denosumab has also been shown to be superior to zoledronic acid in women with breast cancer and bone metastases.

H&O What are the unmet needs in this field?

MS There remains a major unmet medical need for prevention of bone metastases. There are 2 general approaches to this issue. The standard approach has been to treat the underlying malignancy. A second complementary approach is to target the bone specifically, and by doing so, delay or prevent bone metastases. With an international group of investigators, we completed the first successful trial for metastasis prevention using denosumab. This global study of men with castration-resistant, nonmetastatic prostate

cancer showed that treatment with denosumab significantly increased bone metastasis-free survival. We believe this observation may provide a meaningful therapeutic option for patients with castration-resistant prostate cancer.

Suggested Readings

Fizazi K, Carducci M, Smith M, et al. Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: a randomised, double-blind study. *Lancet*. 2011;377:813-822.

Smith MR, Saad F, Coleman R, et al. Denosumab and bone-metastasis-free survival in men with castration-resistant prostate cancer: results of a phase 3, randomised, placebo-controlled trial. *Lancet*. 2012;379:39-46.