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BONE METASTASIS & OSTEOPOROSIS — Bone Metastases In Prostate Cancer And Therapy With Zometa

If a man's prostate cancer is not cured by primary therapy there is a greater than 70% likelihood that during the course of his illness he will experience metastases to bone and suffer morbidity and possibly mortality from this spread. In current literature the consequences of bone metastases are grouped under the term "skeletal related events (SRE)": pathological fractures, spinal chord compression, hypercalcemia, and the need for palliative radiotherapy. The median survival for men after a SRE is about 1 and 1/2 usually symptomatic years.

Why is bone - usually the axial skeleton, ribs, and proximal extremities such a preferred site of metastatic spread? One predisposing factor is the copious blood flow to these areas of red marrow offering ample exposure to circulating cancer cells. But the liver and lungs also are heavily perfused and yet are much less successfully colonized. Intriguing evidence suggests that chemotactic beacons from the bone guide cancer cells to selectively home to marrow stromal cells and the bone matrix. Once there, prostate cell adhesion molecules - a variety of integrins - stick to their matching ligands ... and a metastases is born. The expanding cluster of malignant cells in association with their stromal counterpart drastically alter the local bone metabolism, promoting angiogenesis and releasing bone resorbing factors, and disrupt the delicate balance between the bone building osteoblasts and lytic osteoclasts that governs the constant remodeling of bone.

Osteoclasts nest in pockets in extracellular bone matrix like fists in baseball mitts and a tight interface is essential for facilitating the lytic proteases to break down the collagen matrix. Embedded in this matrix are immobilized cytokines - transforming growth factor *beta*, insulin-like growth factors, fibroblast and platelet-derived growth factors - which are released into the local region. Unfortunately, these very bone derived factors have an proliferative effect on invading cancer cells. The paracrine secretion of cytokines from cancer cells and stroma have a stimulating effect on the osteoclasts leading to a vicious circle of osteolysis. Despite the conventional association of the term "osteoblastic" with the bony lesions of prostate cancer there is abundant ongoing osteolysis. There is evidence that bone resorption precedes bone formation.

The bisphosphonates potently inhibit osteoclastic bone resorption and two major subtypes are (1) non-nitrogen containing, such as the familiar Fosamax, and (2) nitrogen containing, such as the earlier Pamidronate and the current, 1000 times more potent, Zometa. Bisphosphonates, analogues of pyrophosphate, are avidly attracted to the hydroxyapatite particles of bone, replacing pyrophospate. Because of this avidity, a bisphosphonate serves as the bone targeting agent for the 99m-Technetium bone scan. The bisphosphonates home to the osteoclast/bone matrix interface of the pocket and inhibit osteoclastic activity and possibly promote osteoclast apoptosis. The bisphosphonate is released only when resorption or metastatic invasion occurs. Additionally, early evidence suggests that Zometa may be antiangiogenic, decrease tumor invasiveness and adhesion to bone, and inhibit proliferation and induce apoptosis of malignant cells.

The organic matrix of bone is 90% type I collagen - laid down by osteoblasts - and its dissolution is conveniently measured by analyzing the quantity of the urinary excretion of the collagen breakdown fragment, type I collagen cross-linked N-telopeptide (NTX), which is proportional to the total extent of bone lysis. Zometa, a nitrogen containing bisphosphonate, performs one, possibly two, major functions: it inhibits resorption at the osteoclast/matrix interface, but additionally there is evidence accumulating that it also may poison osteoblasts, interfering with cell signaling and effecting apoptosis, and in the same maner may be cytocidal to nearby prostate cancer cells.

Androgen deprivation (AD) stimulates osteoclastic activity and the associated loss of bone mineral density. Dr. Higano, at the University of Washington, was among the authors who, having searched the electronic literature for the accumulated data, published "Osteoporosis in men with prostate carcinoma receiving androgen deprivation therapy", Cancer 2004, Mar 1. They reported a 2% to 8% bone loss in the lumbar spine and a 1.8% to 6.5% loss in the hip over a 12 month period, and recommended that "clinical management should be dictated by the results of radiographic and DXA skeletal assessment". Baseline DXA scans seem appropriate, if not for every man, at least especially indicated for those who are at high risk for incurring osteoporosis (T score > 2.5) during ensuing AD therapy, i.e., men with a family history of osteoporosis, heavy alcohol intake or heavy smoking, low body weight, corticosteroid usage, or significant co-morbidities. Dr. Oliver Sartor, a prostate cancer specialist at LSU Medical Center, recommends repeating the DXA scan yearly during AD therapy and he tailors management based on the results. In another article Dr. Higano reported a 4.5% bone loss in the lumbar spine and 2.5% in the hips over the initial 9 months in a program of *intermittent* AD therapy. At the end a median "off" period of 8 months a 1.5% recovery was seen at the L/S spine, but there was no significant improvement at the hip. Since the occurrence of pathologic fractures are inversely proportional to bone density, there is a need to control bone loss in men whose testosterone is lowered by treatment.

The measurement of urinary N-telopeptide (uNTX-I) can monitor the extent the lytic process. A value of less than 50 nmol/mmol urinary creatinine ("units") is normal for healthy young adults and < 100 units was chosen arbitrarily to divide "low risk" from "high risk" (> 100 units) in men on AD therapy in the excellent article by Brown et al (JNCI, January 5, 2005), "Bone Turnover Markers as Predictors of Skeletal Complications in Prostate Cancer, Lung Cancer, and Other Solid Tumors". The frequency of

adverse outcomes in 203 men under treatment for metastatic prostate cancer (excluding anti-resorptive agents) was reported using this < 100 vs. > 100 cut off point. The outcome events analyzed were SRE, bone disease progression and death. Baseline uNTX-I values > 100 units were predictive of a negative outcome. Over a 24 month period the > 100 unit group had a 3.25 relative risk (RR) for SRE compared to the <100 cohort, and a 2.02 RR for disease progression. The median survival for the entire prostate cancer group was 16.8 months, but when stratified for baseline uNTX levels survival in the < 100 unit group was 22.8 months vs. 11.9 months for > 100 units. If the predictive values of uNTX measurement can be further validated, this test might be applied to men with prostate cancer at a time of less tumor burden and serve as a guide to earlier therapeutic intervention.

Smith (J.Urol June 2003) reported benefit of Zometa treatment in preserving bone density in an early intervention trial that studied men with no distant metastases who were beginning androgen deprivation therapy: "Randomized Controlled Trial of Zoledronic Acid [Zometa] to Prevent Bone Loss in Men Receiving Androgen Deprivation Therapy for Nonmetastatic [M0] Prostate Cancer". A total of 106 men were divided between treatment for one year with Zometa 4 mg every *three months* or a placebo. Mean bone mineral density in the lumbar spines of the treated group showed a 5.6% *increase* compared to a *decrease* of 2.2% in the placebo cohort; and in the femoral neck there was a 1.2% increase vs. a 2.1% decrease.

The currently standard use of Zometa is in treatment of prostate cancer patients with demonstrated skeletal metastases. The long-term benefits of this strategy were presented by Saad et al (JNCI June 2, 2004) in "Long-Term Efficacy of Zoledronic Acid for the Prevention of Skeletal Complications in Patients with Metastatic Hormone-Refractory Prostate Cancer". They report results at 24 months of 122 men who completed a total of months on study. Zometa 4-mg was administered via a 15-minute infusion every *3 weeks* for 15 months as compared a placebo. A SRE developed in 38% of the treated group versus 49% for controls, and in the Zometa arm the *first* new lesion occurred at a median of 488 days versus 321 days in the control group. Subsequent correspondence regarding this article pointed out an unusual, and currently unexplained, development of avascular necrosis of the jaw with prolonged use of Zometa and cited that "osteopetrosis, a disease characterized by pain, mandibular osteomyelitis, and recurrent fractures has been reported during prolonged use (i.e., > 24 months) of certain [nitrogen containing] potent bisphosphonates."

A discussion of the intriquing possibility that nitrogen- containing bisphosphonates have anti-cancer activity will have to await more data. However, a model exists for this possibility. There is strong belief that in the treatment of myeloma Zometa has an anti-proliferative and apoptotic action on myeloma cells, and early data suggests that Zometa may have a similar effect upon prostate cancer cells.

[References are available upon request]

Bottom Line:: The benefits of the bisphosphonate Zometa in the treatment of advanced prostate cancer is well established. Studies suggest that its earlier application can prevent bone loss from androgen deprivation and prevent and postpone deleterious skeletal complications with their attendant morbidity.

PATHOLOGY: High Grade Prostatic Intraepithelial Neoplasia - One last word (for now).

Since the extended discussion of HGPIN in the December issue of PCa Commentary, a report on this subject by Moore et al, Albany Medical College, was published (J Urol, Jan 2005) that is worthy of brief mention: "Prognostic Significance of HGPIN and Atypical Small Acinar Proliferation [ASAP] in the Contemporary Era." The essence of their observation is that there is a marked decrease in the likelihood of finding cancer on repeat biopsy *if* the initial diagnosis of HGPIN had been found in a 10 to 12 core biopsy, now the contemporary practice. On the first repeat extended biopsy performed at a median of 4 months cancer was found in only 1 of 22 men (4.5%) with prior HGPIN, in contrast to quotations of a

25% to 50% risk when sextant biopsies had been done. Eleven of these men underwent a second repeat extended biopsy within a year and no cancer was found. The authors acknowledged that their study was small, but by combining their results with the larger extended biopsy studies of Lefkowitz and the M.D.Anderson Cancer Center "only 3 of 103 (2.9%) men with HGPIN would have been found with cancer on repeat biopsy".

The findings on repeat extended biopsy were very different for men with a initial diagnosis of ASAP, defined as the "presence of suspicious glands with insufficient cytological or architectural atypia for a definitive diagnosis of cancer". On first repeat biopsy cancer was found in 19 of 53 (36%), and in 3 of 19 (l6%) on the second repeat biopsy.

Bottom Line: The current practice of these Albany physicians after finding HGPIN on an initial extended biopsy is not performing a repeat biopsy, but instead following with yearly PSA and DRE.

USEFUL SOURCES OF INFORMATION

Society Of Urologic Oncology Position Statement: Redefining The Management Of Hormone-Refractory Prostate Cancer (CANCER, January 1, 2005, Vol. 103, pp. 11- 21.)

This nine page consensus statement, developed by eleven leading specialists (including Dr. C. Higano, University of Washington) with subsequent peer review, is a succinct and topically organized up-to-date listing and discussion of treatment options. The authors define HRPC broadly as the disease state in which PSA and/or clinical disease progression develops during hormone therapy despite castrate levels of testosterone.

The article is a handy reference for the clinician. It can serve as a mental check list to ensure that the full range of validated options are considered when faced with decisions in patient management. Strategies for various situations are covered efficiently and often in several sentences, but are well referenced as a guide for the search for more detailed information. Sections on "Adjunctive Therapies", "Bone Targeted Therapies", and "Hormonal Manipulation: Second-Line Hormonal Agents" are examples of topical divisions. When compared to the NCCN Internet guideline presentation for HRPC (nccn.org), this consensus article seems more user friendly and informative.

Bottom Line: The Urologic Oncology position statement could serve clinicians as a useful quick office reference source for management options in the treatment of HRPC.