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HORMONE INTERVENTION: Osteonecrosis of the Jaw, Androgen Deprivation, and Bisphosphonates

An article in the May issue of the Journal of Clinical Oncology, "Randomized Controlled Trial of Annual Zoledronic Acid to Prevent Gonadotropin-Releasing Hormone Agonist-Induced Bone Loss in Men with Prostate Cancer" demonstrated in osteoporotic men (T score ≥ -2.5) on ADT with non-metastatic disease that a single dose of 4 mg of the bisphosphonate, Zometa, *increased* bone mineral density after one year by 4.0% vs. a 3.1% *loss* in the placebo arm. This finding will likely further increase the use of this class of drug in prostate cancer.

Current clinical practice guidelines now endorse the use of a much higher dosage regimen, i.e. 4 mg IV every three weeks in men with objective bone metastases, a therapy used with regularity. The finding in the JCO study that by comparison such a minimal exposure as 4 mg *yearly* of this bisphosphonate yields real benefit in the avoidance of androgen deprivation (AD) related bone loss is very good news. An excess of 200 case reports have suggested that heavier dosing and/or long-term usage of bisphosphonates is associated with a rare, but significant toxicity: osteonecrosis of the jaw (ONJ). The principal affected site is the mandible. No clinical trials have as yet established the true incidence of this complication, but based on these case reports, an initial estimate is between 1% and 10%.

A comprehensive review of this issue, "Osteonecrosis of the Jaw in Cancer Patients Receiving IV Bisphosphonates", was presented by Poznak and Estilo, in Oncology, August 2006. The mechanism leading to the bone destruction underlying this pathology is not understood, but suppositions invoke the possibility that the inhibition of osteoclast function by these drugs "may predispose bone to delayed bone remodeling", as might occur after dental extractions. The condition usually involves exposed bone in the maxilla or mandible. Other explanations include disruption of bone microarchitecture, or inflammation/infection as contributing factors. In this regard it may be relevant that AD triples the risk of periodontal disease (Urology 2007;177).

"Although it is often associated with a recent dental surgical procedure, spontaneous ONJ can also occur. Patients commonly present with symptoms such as "pain, drainage, swelling, and anesthesia/paresthesia." The exposed bone appears "necrotic and non-vital." Evidence of bony destruction can be seen on CT/MRI images and increased tracer uptake is seen at those sites on bone scans. "Histologically necrotic bone with associated *Actinomycetes* colonization is often seen. Soft tissue or gingival biopsies reveal inflammed squamous mucosa or granulation tissue."

The incidence increases with the duration of treatment. The review noted that "the median time to ONJ in patients [receiving bisphosphonates] with metastatic breast cancer or multiple myeloma to be 39 to 72 months in those treated with pamidronate [Aredia] and 18 months in those treated with zoledronic acid [Zometa]." Other studies found a lesser incidence of ONJ with pamidronate therapy. A better estimate of incidence will likely emerge from the inclusion of monitoring for ONJ in two upcoming trials using long-term bisphosphonates in breast cancer.

A report (Leukemia. 2007, Apr 5),"A different schedule of zoledronic acid can reduce the risk of osteonecrosis of the jaw in patients with multiple myeloma" compared the occurrence of ONJ in one group of patients receiving monthly bisphosphonate therapy until intolerance, to a group that received monthly treatment for one year and then every three months thereafter. The incidence of adverse skeletal events was similar, but the reduced schedule group had an eight-fold reduction in ONJ. ONJ was higher in those receiving Zometa vs pamidronate (9.1 vs 1.6 per 100 person years).

ONJ is not confined to those persons receiving the more potent bisphosphonates, pamidronate or zoledronic acid. Alendronate (Fosamax) and risedronate (Actinel) are commonly used as long-term therapy for cancer-unrelated osteoprosis. A March 20, 2007 report in the Annals of Internal Medicine evaluated the use of Fosamax in prostate cancer: "Effect of once-weekly [70 mg] oral alendronate on bone loss in men receiving androgen deprivation [ADT] therapy for prostate cancer: a randomized trial." This study of 112 men with non-metastatic cancer receiving ADT therapy found that "In men treated with alendronate, bone mineral density increased at 1 year by 3.7% at the spine and 1.6% at the femoral neck." The respective figures for the placebo group were *losses* of 1.4% and 0.7%. The observation that "At baseline, 39% of men had osteoporosis and 52% had low bone mass" just underscores the recommendation that all men undergo a DEXA study before starting ADT.

The dental community is very sensitized to the risk of ONJ posed by bisphosphonate useage since they are the professionals who perform the dental surgery and are called upon to treat the condition. The Oncology review points out the obvious, that "Oral health is an important component of the patient's overall care" and recommends a dental assessment prior to the start of antiresorptive drugs. There is no standard treatment for ONJ. "General approaches to managing ONJ include the use of antibacterial rinses, conservative and minimal debridement with focus on removing sharp edges of bone, and antibiotic therapy if superinfection is present."

Bottom Line: For the oncology community, the important message is to be aware of the risk of the infrequent occurrence of osteonecrosis of the jaw associated with bisphosphonate useage during ADT therapy. This knowledge should lead to the regular inspection of the oral cavity and an inquiry about symptoms in every person on long-term bisphosphonate treatment.

DIAGNOSTICS: PROSTASCINT SCAN: 27% Positive Predictive Value for Detecting Prostate Cancer Outside the Prostate Bed in Men with Rising PSA Following Primary Therapy.

The question is frequently raised in tumor board discussions as to the effectiveness of a ProstaScint scan in detecting metastatic disease. This issue is addressed in a Loyola University study, "Long-term follow-up of 111 In-capromab pendetide (ProstaScint) scan as pretreatment assessment in patients who undergo salvage radiotherapy for rising prostate-specific antigen after radical prostatectomy for prostate cancer" (Int J Rad Oncol Bio Phys, Mar 1, 2007).

The test's radiolabled tracer targets to prostate cancer in soft tissues by recognizing an epitope in the transmembrane prostate-specific membrane protein (PSMA), which is "highly expressed in malignant prostate tissue." The study was designed to "evaluate long-term failure patterns" associated with the use of this test as staging prior to salvage radiotherapy. Although other studies have reported differing outcomes for accuracy of the ProstaScint, the authors point out that their study involves the largest cohort with the longest median follow-up for evaluation of the test.

The 4-year biochemical outcome after salvage radiotherapy to the prostate bed (median dose 66.6 Gy; range 63-70.2) was assessed for twenty patients whose post-RP PSA levels were >0.2 ng/mL, and who, at failure, showed no evidence of metastatic disease on CT and isotope bone scanning. The median follow-up was 41 months from salvage RT; the median Pre-RT PSA was 0.4 ng/mL. Their findings: The 4-year bRFS for patients with negative scans was 53%; for scans positive in the prostate bed only, 45%; or for scans positive elsewhere, 74%. There was no significance in these different results. (p=0.51)."

One study observation was confirmatory to current salvage RT strategy: "... a pre-RT PSA level of less than 1 ng/mL was the only factor predictive for improved bRFS."

Study conclusion: "Although the capromab pendetide scan revealed regional or distant uptake in approximately one-third of the patients, the bRFS in this group did not differ from those whose scans showed no or local uptake only," i.e. "a positive ProstaScint scan beyond the prostate bed had no effect on the 4-year bRFS."

DIAGNOSTICS: "PCA3 Molecular Urine Assay for Prostate Cancer in Men Undergoing Repeat Biopsy", Urology 69(3),2007

In this article a consortium of researchers, including Dr. Bill Ellis, University of Washington, report the evaluation of the performance of newest iteration of this assay. The earlier version, UPM3, was reviewed in the April 2006 PCa Commentary: "UPM-3 A diagnostic urine test with greater accuracy for cancer detection than PSA. The biologic basis of the test is the identification in urine of an epitope on mRNA from the PCA3 gene, a gene "highly overexpressed in PCa tissue compared with benign prostate tissue." The PCA3 test quantitates the ratio of the number of copies of PCA3 mRNA to those of mRNA for PSA, the latter taken as a representative surrogate for the totality of benign and malignant prostate tissue. A test result is presented along a continuum range of <5 to >100. Statistical analysis suggested a score of 35 as the optimal cutoff, which "provided high specificity (72%), preserved sensitivity (58%), and yielded an odds ratio of 3.6." A PCA3 score of <5 was associated with an ~11% likelihood of a positive repeat biopsy; a score between 20-34, ~22%; and between 50 and 100, an ~45% likelihood.

The goal of the study was to compare the efficiency of the PCA3 test against the standard PSA (at a comparison cut-point of 4 ng/mL) in predicting the likelihood of finding cancer on a repeat biopsy in men whose initial PSA values had triggered a biopsy, but in whom at least one previous 12-core biopsy had been negative. Urine specimens from 226 men whose PSA values were > 2.5 ng/mL were studied (median PSA: 6.1 ng/mL ; range 2.5 - 31.1). The specimens were informative in 97% of the men. Cancer was found in 60 (27%) on repeat biopsy.

In a comparison based on their respective "areas" plotted on the receiver operating curve graph, the performance of the PCA3 test showed greater predictive efficiency, 0.678, vs. 0.524 for PSA, the latter "indicating little better than a 'coin toss' probability of predicting the presence of CaP."

As stated in the article, "25% of CaP cases remain undiagnosed after a single set of core biopsies." Improved predictability of detection could reduce the morbidity and expense of the exercise of re-biopsy by permitting greater selectivity

For further information about obtaining the test material and processing contact the Bostwick Lab representative, Ms. Bonnie Scott, at 206-853-2573

Bottom Line: The authors conclude: "For men with elevated serum PSA levels who are undergoing repeat prostate biopsy, the PCA3 assay appears to represent an incremental improvement in the ability to predict the prostate biopsy outcome."

DIAGNOSTICS: "EPCA-2: A Highly Specific Serum Marker for Prostate Cancer," UROLOGY 69:714-720,2007.

Drs. Robert Getzenberg, Alan Partin et al., working at the University of Pittsburgh and Johns Hopkins University, in this article describe the early developmental studies suggesting greater specificity of a new biomarker, EPCA-2 (Early Prostate Cancer Antigen-2) as compared to the standard PSA for detection of "overall prostate cancer." Their new test also was "highly specific in discriminating between people with and without prostate cancer." An additional assay attribute permitted "differentiating between localized and extracapsular disease." EPCA-2, an epitope residing in "nuclear structural elements of prostate cancer cells", is measurable in serum, and the initial studies used a cutoff set at 30 ng/mL.

The test was validated by analyzing EPCA-2 levels in six categories of people - all told 330 individuals: a collection of men with and without cancer whose PSA values were less than 2.5 ng/mL; men with localized or non-organ confined disease, or BPH; and a diverse group of controls. In 98 men with no evidence of cancer or a negative prostate biopsy whose PSA levels were <2.5 ng/mL, and in 35 men with BPH, the specificity of the new test was 92% vs. 65% for PSA. Its sensitivity was 94% in 80 men with local or non-organ confined cancer.

The assay for EPCA was "highly accurate in separating men with organ confined disease from those with non-organ confined disease" as determined by receiver operator characteristic curves. Additionally, the study included evaluation of pre- and post-prostatectomy assays in ten men. The initially elevated PSA and EPCA-2 values in these men fell in tandem, with all PSA values dropping to <0.1 ng/nL; and their elevated EPCA-2 values also showed a matching drop to comparably low values. The assay is being further refined to lower the background test noise so as to yield a result that more selectively reflects prostate cancer. In an interview (Health Day News) Dr. Getzenberg was quoted as summarizing the performance of the test by saying "a specific level of EPCA-2 identified 90 percent of men with cancer confined to the prostate and 98 percent of those in whom it had spread beyond the gland. The test was negative in 97 percent of men without prostate cancer."

It is premature to consider the use of this test in screening studies. Considerable further validation is in order. But there is promise that the EPCA-2 test will offer advantages superior to our historic PSA test.