Drug-Induced Bone Loss: An Increasing Problem for Men with Prostate Cancer

Because testosterone promotes the proliferation of many types of prostate cancers, suppression of its androgenic effects has become a primary target for prostate cancer drug therapies. Androgen-suppressing drugs, such as the widely used luteinizing hormone–releasing hormone (LHRH) agonists reduce free testosterone, thus eliminating a major driver of cancer cell growth.

However, testosterone is also responsible for maintaining bone mineral density (BMD) in men, and rapid BMD loss is an unfortunate side effect of treatment with these drugs. The loss occurs within months of exposure, often rendering men osteoporotic with a markedly increased risk of fracture within one to two years of treatment. For patients who begin these therapies and already have low BMD, this situation may be particularly problematic.

Over the last decade, a number of studies have shown that androgen-deprivation therapy (ADT) reduces BMD at a rate of 2% to 7% per year, reported Tracey Krupski, MD, MPH, of the Department of Urology at UCLA's Geffen School of Medicine in Los Angeles. Dr. Krupski presented an analysis of Medicare data from more than 50,000 men, noting that the loss of BMD translates directly into a rise in fracture rates. In this study, the rate of fractures over a five-year period was 19.3% for patients receiving ADT, compared with a rate of 12.6% for a group of similar men not receiving ADT. The hospitalization rate for fractures was 5.1% for men using ADT versus 2.3% for non-users. Greater drug exposure correlated directly with greater fracture rates.

“Many of these patients lose their independence, ending up in long-term care facilities,” said Dr. Krupski.

Matthew R. Smith, MD, and colleagues at Harvard Medical School presented data from more than 12,120 anonymous prostate cancer health insurance claims from Fortune 500 corporations. They found an alarming 13% increased risk of all types of fractures among men receiving gonadotropin-releasing hormone (GnRH) agonists such as leuprolide (Lupron®, TAP) and goserelin (Zoladex®, AstraZeneca). The risk of hip fractures was increased by 39%, and the vertebral fracture risk was increased by 22%. Mei Sheng Duh, ScD, also of Harvard Medical School, who presented the data for Dr. Smith, emphasized that these figures are conservative.

Christopher Ryan, MD, from the Oregon Health and Science University in Portland, presented data from prostate cancer patients treated with ADT for less than 12 months. The men underwent BMD assessments prior to randomization to either placebo or zoledronic acid (Zometa®, Novartis), 4 mg intravenously every three months for one year, in addition to ongoing ADT. Overall, 66.7% of the men were either osteopenic or frankly osteoporotic following ADT. Bone loss was higher at the femoral neck than at the lumbar spine or the total hip.

Median exposure to androgen-suppressing drugs in this cohort was only three months, suggesting that the loss of BMD occurred shortly after the onset of androgen suppression. The degree of bone loss correlated strongly with the duration of exposure.

The investigators studied many variables that might have affected BMD. They found that increased body mass index, calcium and vitamin D supplementation, exercise, and, surprisingly, alcohol consumption, were all associated with higher BMD and a lower risk of ADT-induced osteoporosis. Dr. Ryan had no explanation for the positive effect of alcohol (contrary to other evidence showing a direct relationship between alcoholism and osteoporosis), but he noted that a similar pattern has been observed in studies of osteoporosis in postmenopausal women.

Earlier trials have also shown zoledronic acid had the potential to counter the bone-depleting effects of ADT. The precise role of this drug in treatment strategies, Dr. Ryan added, should be much clearer when this 19-center trial is completed in the near future.

The synthetic hormone bicalutamide (Casodex®, AstraZeneca) is a nonsteroidal antiandrogen that inhibits the action of testosterone without reducing testosterone levels. In light of data showing that bicalutamide does not induce BMD loss,
it is likely to play an increasing role in the treatment of hormone-sensitive prostate cancers, according to Vivek Wadhwa, MD, from Arrowe Park Hospital in Wirral, United Kingdom. Bicalutamide is unique in that it works by blocking testosterone receptors on the surface of prostate cancer cells, thus preventing the cell proliferation signal without lowering actual testosterone levels.

Dr. Wadhwa and colleagues studied 430 men with locally advanced or metastatic prostate cancer. Those men who were already osteoporotic at the baseline assessment were treated with bicalutamide plus calcium and vitamin D supplements. Those who had normal BMD or who were osteopenic received LHRH analogues. All patients were followed for five years.

The men with normal baseline BMD showed a marked loss of BMD beginning shortly after treatment with LHR agonists. Mean T-scores, a measure of BMD, went from −0.25 at the baseline (within normal range) to −1.52 by the fourth year, indicating that the majority of patients had become osteopenic.

In the men who started out with osteopenia, LHRH agonist treatment had the effect of moving 60% of them into the osteoporotic range within two years. Mean T-scores dropped from −1.72 at baseline to −3.78 by the fourth treatment year. In contrast, the patients receiving bicalutamide showed no significant change in BMD over the course of the study. The mean T-score at baseline was −3.54 in this cohort; by the fourth year, it was −3.78, a nonsignificant decrease.

Dr. Wadhwa and other researchers at the AUA meeting called for routine measurement of BMD prior to initiation of any antiandrogenic therapy for prostate cancer. In many cases, a drug like bicalutamide, or the addition of a bisphosphonate and vitamin D and calcium supplementation, can help prevent debilitating fractures, especially in men with a low BMD before the beginning of treatment.

**Are Bone Scans Always Necessary in Early Prostate Cancer?**

Many physicians who treat men with prostate cancer routinely order bone scans in an effort to predict the likelihood of bone metastases. According to Gerald Chodak, MD, of the Prostate and Urology Health Center at Weiss Memorial Hospital in Chicago, Illinois, a large number of these scans are unnecessary.

He believes that in the absence of other indicators of metastasis, bone scans give little useful information in men with early-stage prostate cancer. He based his assertion on data from the ongoing Early Prostate Cancer (EPC) study, which involves more than 8,000 men with nonmetastatic disease. An analysis has clearly shown that for men who have undergone radical prostatectomy or radiation therapy, bone scans are not warranted unless prostate-specific antigen (PSA) levels exceed 5 ng/ml. When “watchful waiting” is the chosen course, a bone scan is unnecessary unless the PSA exceeds 20 ng/ml, Dr. Chodak said.

“Many clinicians are ordering [the scans] if the PSA increases over two to three visits, even if the actual PSA level is low. They’re ordering the test because they’re afraid not to,” Dr. Chodak continued. “It is understandable to want to rule out metastasis before starting treatments, but this [bone scan] is not the test to get.”

Dr. Chodak’s study included 8,113 men; 4,061 of them were randomly assigned to receive placebo, and 4,052 were assigned to receive bicalutamide 150 mg/day, in addition to radiation therapy or prostatectomy. The men were observed for a median of 5.4 years. A total of 5,048 patients underwent pre-treatment bone scans. There were 148 positive scans (2.9%) in the patients taking placebo. In those patients whose baseline PSA was below 5 ng/ml, the rate of positive scans was only 0.8%. The number jumped to 3.5% in men whose PSA ranged from 10 to 20 ng/ml and rose further to 6.3% with PSAs in the range of 20 to 50 ng/ml. There were slight variations, depending on whether patients had radiotherapy or surgery, but the overall pattern was the same for all treatment groups.

Patients receiving bicalutamide had a lower overall positive scan rate of 1.6%. When the PSA was under 5 ng/ml, the positive scan rate was 0.4%. This figure increased to 6.3% among the men in the 10- to 20-ng/ml range, and it rose further to 11.6% for those with PSAs in the range of 20 to 50 ng/ml.

In summary, Dr. Chodak held that the positive scan rate among the men with low PSAs was too small to justify the high cost of tests that nearly invariably come back negative. Pointing out that there is no definitive method for predicting or ruling out bone metastases in men with early-stage prostate cancer, Dr. Chodak speculated:

“It may turn out that PSA doubling may be the best criterion. If your PSA doubles in less than six months, there’s an increased risk of bone metastases, but we have no randomized trials yet.”

He said that the EPC study showed that bone scans are largely pointless if the PSA is less than 5 in treated patients or below 20 in untreated men.

**Can Genetics Guide Drug Choice in Prostate Cancer? Not Yet**

Will genetics soon guide drug treatment choices for the treatment of prostate cancer?

Avi Retter, MD, of the National Cancer Institute’s Medical Oncology Clinical Research Unit in Bethesda, Maryland, has been examining the ways in which an individual’s genetically determined metabolic predispositions predict response to drug therapies. Specifically, he and his colleagues are studying the relationship between mutations in genes that code for various cytochrome P450 (CYP450) enzymes and response to prostate cancer drugs. These enzymes, produced in the liver, catalyze the biochemical pathways through which many drugs are metabolized. In cancer chemotherapy, he said, a greater ability to metabolize drugs would presumably enhance response and improve survival while genetically determined deficiencies in metabolic enzyme production would lower the response rate.

Dr. Retter’s study looked at genes coding for the CYP3A4 enzyme, which plays an important role in the metabolism of thalidomide, a commonly used adjunct drug for prostate cancer. Thalidomide must be transformed into its active form through hepatic metabolism. The study involved 73 men with androgen-independent prostate cancer who received thalidomide 200 mg daily plus the antineoplastic agent docetaxel (Taxotere®, Aventis) 30 mg/m² for three of four weeks or docetaxel alone. Overall, those receiving combination therapy survived longer: median survival in the docetaxel/thalidomide
arm was 25.9 months and 14.7 months for those who were taking docetaxel alone.

The primary investigation into the extent to which polymorphisms in the gene coding for CYP2C19 predicted survival, somewhat surprisingly, failed to detect significant differences. Comparing mean survival of men with genes for the wild-type CYP2C19 with those who had CYP2C19 mutations, Dr. Retter found no strong correlation between survival and genotype.

Median survival among 14 of 48 men with CYP2C19 mutations receiving thalidomide was 19 months; for the 34 men with the wild-type CYP2C19, it was 26 months. The difference was not statistically significant. Equally surprising was the observation that in the docetaxel monotherapy group, men who had the wild-type CYP2C19 showed a trend toward improved survival over those with the mutation, even though the CYP2C19 enzyme is not thought to play a role in docetaxel metabolism.

Although the CYP2C19 genotype did not ultimately prove to be a good predictor of survival, Dr. Retter said that there are many other enzymes in the CYP450 pathways that are worthy of investigation.

“This is a step in the direction of choosing therapies based on genetic factors influencing drug metabolism. That is ultimately where we want to go with this.”