

Prostate Ca: Annual Zoledronic Acid Protects Bone

Prostate cancer patients taking androgen-deprivation therapy had higher BMD after the Zometa treatment.

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ATLANTA — An annual dose of zoledronic acid can prevent bone loss in men undergoing androgen-deprivation therapy for nonmetastatic prostate cancer, Dr. M. Dror Michaelson reported at the annual meeting of the American Society of Clinical Oncology.

Investigators randomized 40 men who were being treated with gonadotropin-releasing hormone (GnRH) agonists to a single 4-mg intravenous dose of zoledronic acid (Zometa) or placebo.

Twelve months later, the men treated with zoledronic acid had average bone mineral density (BMD) increases of 4% in the lumbar spine and 0.7% in the total hip. The placebo group lost 3.1% of BMD in

the lumbar spine and 1.9% in the total hip.

Two bone turnover markers, serum N-telopeptide and bone alkaline phosphatase, decreased during this same period in the men given zoledronic acid and increased in the placebo group. The differences were statistically significant.

"Annual zoledronic acid should be considered in GnRH-agonist treated men who may be at risk for osteoporosis," Dr. Michaelson, of Massachusetts General Hospital Cancer Center, said on behalf of coinvestigators from his institution and the Dana-Farber Cancer Institute, both in Boston.

Dr. Michaelson said concern about side

effects drew the group to explore annual dosing as an alternative to more frequent bisphosphonate use in these patients.

GnRH agonists are known to decrease bone mineral density while increasing bone turnover and fracture risk. Studies have shown that pamidronate as well as zoledronic acid can increase BMD in prostate cancer patients receiving hormonal therapy.

Concern about side effects prompted researchers to explore annual dosing as an alternative to more frequent bisphosphonate therapy in these patients.

Frequent bisphosphonate use can cause serious side effects, however, particularly renal insufficiency and osteonecrosis of the jaw. An annual dose of zoledronic acid had been shown to prevent bone loss in postmenopausal

women, but Dr. Michaelson said the strategy had not been tested in men.

The trial excluded prostate cancer patients with metastatic bone disease, prostate-specific antigen evidence of pro-

gression, or osteoporosis. The men enrolled had an average age in the mid-60s. All patients in both arms of the study were encouraged to take daily supplements of calcium and vitamin D, Dr. Michaelson said.

In a discussion of the trial, Dr. Ian F. Tannock said the biomarkers were a reasonable surrogate end point for fracture risk. Although small, the trial probably was large enough to produce significant findings, he said, noting that the results are consistent with those of other studies. "I think those conclusions are reasonable," said Dr. Tannock, the Daniel E. Bergsagel professor of medical oncology at Princess Margaret Hospital and the University of Toronto.

Estimating the cost of 4 mg of zoledronic acid to be about \$600, he asked whether less-frequent dosing also could be effective in men with metastatic prostate cancer. "I think we should consider using that very expensive medication less often in that group of men, also," he said.

Novartis Oncology and the Prostate Cancer Foundation supported the study. ■

Heparin Fails to Cut Rate of DVT/PE After Prostatectomy

PARIS — Prophylactic use of heparin made no difference in the incidence of symptomatic deep vein thrombosis and/or pulmonary embolism after 4,609 laparoscopic radical prostatectomies reviewed by the International Laparoscopy Prostate Cancer Working Group.

Eleven centers in seven countries contributed patients to the ongoing study. Dr. Fernando P. Secin presented an interim analysis of the study data at the annual congress of the European Association of Urology.

The overall rate of deep vein thrombosis and/or pulmonary embolism (DVT/PE) was low: 0.6%, according to Dr. Secin, a urology fellow at Memorial Sloan-Kettering Cancer Center in New York.

Dr. Secin speculated that most patients undergoing laparoscopic radical prostatectomies are probably at low risk for thromboembolic events.

"Most prostate cancers [that] are operated [on] are early prostate cancers, so the impact of the cancer itself on the thrombotic mechanism may not be that serious," he said in an interview at the meeting.

Although heparin use was not a statistically significant factor in univariate or multivariate analyses, the latter did identify the following risk factors as being significant for DVT/PE in patients undergoing laparoscopic radical prostatectomy:

- ▶ Patients undergoing a reexploration were 20 times more likely to have a thromboembolic event.

- ▶ The odds were 13 times greater for those with a prior history of DVT.

- ▶ Every 10-g increase in prostate size raised the odds ratio by 1.2.

The investigators concluded that the

data do not support heparin prophylaxis in patients who do not have these risk factors. Randomized trials are needed to establish its utility, they said.

Centers in France, Belgium, Austria, the United Kingdom, Spain, Sweden, and the United States contributed patients to the analysis. Dr. Secin said he hopes to accumulate another 1,000 patients before completing the study.

Prophylaxis protocols ranged from no heparin use to both preoperative and postoperative use of heparin, with no discernible relationship to the rate of DVT/PE at each hospital. All the institutions used mechanical prophylaxis: either a pneumatic compression device or a gradual compression stocking.

The lowest and highest DVT/PE rates (0% and 1.4%, respectively) were both found at centers that administered heparin before and after surgery. At the Cleveland Clinic, where heparin prophylaxis was not used, the rate was 0.5%.

Patients receiving preoperative heparin had significantly higher intraoperative mean blood loss, compared with those given postoperative heparin or no heparin: 444 mL vs. 332 mL.

This difference in blood loss did not translate into longer hospital stays or higher transfusion or reoperation rates, according to Dr. Secin.

Estimating the cost of heparin at \$80 per dose, the investigators calculated the total cost as \$2,955,057 for the 11 centers that contributed data.

"You spend so much money and there isn't any use for that," said Dr. Bertrand D. Guillonnet, the study's senior author and section head of minimally invasive surgery, department of urology, Memorial Sloan-Kettering. ■

Small Prostate Gland More Likely To Have Positive Surgical Margins

PARIS — Patients with smaller prostate glands were at greater risk of positive surgical margins in a retrospective side-specific study of laparoscopic radical prostatectomies at Memorial Sloan-Kettering Cancer Center in New York.

The finding runs counter to what many surgeons believe, Dr. Fernando P. Secin said in an interview at the annual congress of the European Association of Urology.

In the minds of surgeons, a small gland is an easy case, said Dr. Secin of the department of urology at Memorial Sloan-Kettering. Instead, he reported that a gland weighing less than 30 g was one of seven risk factors identified in the study of 407 patients resected by a single surgeon between October 2002 and April 2005.

The other risk factors were a prostate-specific antigen (PSA) score greater than 10 ng/mL, a biopsy Gleason score of 7 or higher, the presence of bulky disease on endorectal MRI, a palpable nodule, and either multiple positive biopsy cores or a high percentage of tumor on biopsy cores.

Dr. Secin and his coauthors suggested that laparoscopic surgeons might decrease the incidence of positive surgical margins by considering these factors when planning operations.

Neurovascular bundle (NVB) dissection was not found to be a risk factor for positive surgical margins in "adequately selected patients." The study was the first to evaluate the impact of three degrees of NVB on surgical margins, Dr. Secin said.

Patients were significantly more likely (odds ratio 3.85) to have positive margins with an interfascial NVB than with an intrafascial NVB. Positive margins were more common (odds ratio 1.41) with an extrafascial NVB, but the difference did not reach statistical significance.

Another innovative find in the study was the side-specific analysis that excluded any side of a prostate gland that did not contain cancer. As cancer-free sides would always have a negative margin by definition, including them did not yield information about risk factors in these procedures, Dr. Secin explained.

The investigators excluded 86 of 814 evaluable prostate sides, analyzing a total of 728 sides: 361 right sides and 367 left sides. All told, positive surgical margins occurred in 26 right sides (7.2%) and 33 left sides (9%).

The positive margin rate was highest at the apex and the posterior of the gland. Positive margins also were about twice as likely to occur at the apex when tumors were on the left side of the prostate: 15 cases were on the left side (4.1%) vs. 8 on the right side (2.2%). Posterior margins were similar on both sides: 14 occurred on the right side (3.9%) and 11 on the left (3%), he reported.

Dr. Bertrand D. Guillonnet, senior author and section head of minimally invasive surgery in Sloan-Kettering's department of urology, suggested that smaller glands may have larger tumors proportionally. "The remarkable thing is the smaller the gland, the higher the risk," he said. ■



Other risk factors included a PSA level of more than 10 ng/mL and a biopsy Gleason score of 7 or higher.

DR. SECIN