The If’s, And’s, or But’s Regarding Bisphosphonates for Prostate Cancer

Timothy J. Wilt, Kristine E. Ensrud

In 2007, an estimated 218,890 men will be diagnosed with, and 27,050 deaths will be attributed to, prostate cancer in the United States (1). Men with prostate cancer are at increased risk for skeletal related complications. Bony metastases can result in pain, disability, and pathologic fractures. Use of androgen deprivation therapy (ADT) for primary or palliative treatment is associated with an increased rate of bone loss and higher risk of nonpathologic fractures (2). ADT use has increased two- to fourfold in the past 10 years, and up to 45% of white men receiving conservative management for early-stage prostate cancer receive ADT (3). An estimated 3000 excess fractures per year have been attributed to the use of ADT in older men (2).

Bisphosphonates, which are primarily used to treat postmenopausal osteoporosis, are increasingly prescribed for men with prostate cancer because randomized trials suggest that these antiresorptive drugs may reduce skeletal-related events (4–6) in prostate cancer with bony metastases. In addition, trial data demonstrate that bisphosphonates are effective at preventing ADT-induced bone loss and reducing levels of bone-turnover markers (7,8). Consensus statements have advocated monitoring for bone loss with serial bone mineral density (BMD) testing and, if clinically significant bone loss is observed, consideration of bisphosphonate therapy (9). Of greater importance to patients and clinicians is whether these drugs palliate pain, prevent disease progression and clinically recognized fractures (both pathologic and nonpathologic), and improve quality and length of life.

Important evidence has been provided by the Medical Research Council (MRC)-PR04 randomized trial published in this issue of the Journal (10) and a similar protocol previously published by this group involving 311 prostate cancer patients with bony metastases commencing or responding to first-line hormone treatment (MRC-PR05) (4). Although disappointing, the PR04 findings are unequivocally negative. They contrast with prior results from trials and systematic reviews (10,11) evaluating bisphosphonates for other malignancies, prostate cancer with bony metastases (including PR05), and prevention of bone loss in earlier stage prostate cancer. The PR04 results diminish support for routine long-term bisphosphonate use in nonmetastatic prostate cancer even among men receiving ADT.

Examining between-study heterogeneity is potentially helpful for understanding the seemingly discrepant results and facilitating design of future studies. PR04 enrolled 508 men considered at high risk of developing bone metastases due to having locally advanced disease. Both PR04 and PR05 were double blinded and evaluated a high dose of a first-generation oral bisphosphonate, clodronate (1280 mg/day), versus a matching placebo. PR04 treatment was for a maximum of 5 years (PR05 = 3 years), and median follow-up was 10 years. Treatment compliance was similar between the trials, although a lower percentage in PR04 stopped clodronate due to reaching the outcomes of symptomatic bone metastases or death (15% versus 44%). Median prostate-specific antigen (PSA) level at random assignment was 13 ng/mL. BMD measurements were not obtained, and men were not offered vitamin D or calcium.

In PR04, men who were randomly assigned to clodronate had no improvement in the primary endpoint of symptomatic bone metastases or prostate cancer death (median time to event = 107 months with clodronate and 131 months with placebo). Although 95% confidence intervals (CIs) were wide, hazard ratios (HRs) favored placebo for other outcomes, including first progression, local progression, and PSA progression; symptomatic bone metastases; prostate cancer death; and overall mortality. Adverse events and those requiring dose modification were more common with clodronate than with placebo. Results did not vary according to risk subgroups defined at baseline by age, performance status, tumor stage, or PSA level. In contrast to trials enrolling men with established bony metastases, not all PR04 enrollees were receiving ADT. However, subgroup analyses indicated that clodronate was not effective for men receiving ADT alone as primary therapy. Furthermore, the hazard ratio indicated harm with clodronate when ADT was used in combination with radiation therapy (HR = 2.59, 95% CI = 1.33 to 5.03). PR04 strengths include large sample size, median treatment duration of 4 years, long and complete follow-up, clinically relevant primary and secondary outcomes, high number of events (half of enrollees died, 27% from prostate cancer), and use of an adjudication committee blinded to treatment status to assess outcomes.

Population-based estimates indicate that the absolute increase in any fracture among men with prostate cancer surviving 5 years after diagnosis and receiving ADT compared with no ADT is 6.8%. For fractures resulting in hospitalization, the absolute risk is 2.8% (2). PR04 did not provide fracture information. However, the hazard ratio for symptomatic bone metastases was 1.32 (95% CI = 0.91 to 1.93; 23.6% versus 18.5% developed symptomatic bone metastases) in favor of placebo. Therefore, it is unlikely that clodronate improved 10-year overall fracture risk (pathologic + nonpathologic) even among men receiving ADT. Previous bisphosphonate trials evaluating men receiving ADT for nonmetastatic prostate cancer were small, short term, and claimed benefits due to bisphosphonates’ ability to increase or stabilize BMD or reduce levels of bone-turnover markers (9,10). Bisphosphonate trials in men without cancer, but who were judged at increased fracture risk due to low BMD, have also not been adequately
powered to assess clinically detected fractures. Therefore, the effect of bisphosphonates on clinical fractures in men is not known and requires testing in large, long-term randomized trials. These trials should plan to assess fracture outcomes according to risk subgroups prognostic for skeletal complications and mortality, including tumor histology, age, ADT use, and BMD status.

No active-comparison trials of bisphosphonates have been conducted in men with prostate cancer. Adverse effects and tolerability may vary between bisphosphonate type and route of administration. However, it is unlikely that differences in the type, dose, or route of bisphosphonate administration fully explain outcomes. All bisphosphonates improve or slow decline in BMD. Effectiveness in preventing fractures in postmenopausal osteoporosis, improving hypercalcemia of malignancy, and reducing pain and pathologic fractures in breast cancer and multiple myeloma has been demonstrated in prior trials. But clinically relevant efficacy in prostate cancer cannot be inferred from trials evaluating BMD or other malignancies. Bony metastases in prostate cancer, unlike many malignancies, are primarily osteoblastic and not osteolytic in nature.

Clodronate, which is not available in the United States because of concerns about leukemia, has relatively poor absorption and bioavailability. It is less potent and may not be as free of toxicity as other bisphosphonates or if administered intravenously. As described by Mason et al. (10), similar doses of clodronate provided a non–statistically significant improvement in symptomatic bone progression and overall survival in PR05 and reduced bone metastases and improved survival in two of three breast cancer trials. Intravenous pamidronate, a second-generation bisphosphate, stabilized bone loss compared with placebo in men with nonmetastatic prostate cancer receiving ADT (7). However, in two other trials of 378 men with bone pain due to metastatic prostate cancer after first-line hormone therapy, pamidronate failed to palliate pain or reduce skeletal-related events (12). Zoledronic acid, a third-generation bisphosphonate with relative potency 2000-fold greater than clodronate, reduced skeletal-related events in men with bone metastases and hormone-refractory disease when given intravenously at 4 mg every 3 weeks for 15 months. However, this dose did not decrease symptomatic bone metastases (11). Despite some improvement in pain control, there was no difference in disease progression or quality of life. In men randomly assigned to receive 8 mg with subsequent dose reduction to 4 mg due to toxicity, skeletal-related events were not decreased. Nearly half on zoledronic acid withdrew consent or discontinued due to adverse events or unsatisfactory therapeutic effect.

PR04 findings have broad clinical implications because greater than 90% of men with prostate cancer do not have bony metastases at diagnosis. Men who have locally advanced or clinically localized disease have a long life expectancy (median survival = 115 months in PR04 versus 37 months in PR05). Use of prolonged ADT is common and can accelerate bone loss. If BMD testing is performed routinely, many men might be classified as osteopenic (low bone mass) or osteoporotic, especially if criteria are based on measurements at multiple sites and male-specific cutoff values for BMD are used to make the diagnosis (8). Compared with men with metastatic disease, the number of men with nonmetastatic prostate cancer who are potential candidates for bisphosphonate therapy is considerably greater and duration of treatment markedly longer.

Compiled results to date suggest that the effectiveness of bisphosphonates for improving clinically relevant outcomes in prostate cancer is not certain. “If” bisphosphonates are effective, then differences in disease stage and outcomes assessed are the most plausible reasons for differences between PR04 and PR05 and other prostate cancer trials. These results suggest a narrow therapeutic window and the importance of using standardized, clinically relevant outcomes. “And,” PR04 demonstrates that clodronate is not beneficial in men with locally advanced disease. Unless future trials demonstrate effectiveness of other bisphosphonates in improving clinically relevant, rather than surrogate, outcomes, they should not be routinely used in the absence of bony metastases, regardless of ADT status. Routine BMD testing to monitor bone health or establish a threshold for initiating bisphosphonate therapy in men with nonmetastatic prostate cancer has not been demonstrated to reduce fracture incidence. Such practice is not supported by the available evidence. The presence of relatively early bony metastases may be the best predictor to determine whether bisphosphonates provide clinical benefit in men with prostate cancer. “But,” inconsistency across published trials and lack of improvement in length or quality of life using high doses of potent intravenous bisphosphonates does not rule out the possibility that no benefit exists. Additional trials clarifying the role of bisphosphonates in prostate cancer are needed.

References