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EDITORIAL

Bisphosphonate-Related Osteonecrosis of Jaw in the Adjuvant Breast Cancer Setting: Risks and Perspective

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Bisphosphonate-related osteonecrosis of jaw (BONJ) is a rare adverse effect of antiresorptive treatments (primarily zoledronic acid and more recently denusomab) to my knowledge first described 10 years ago. The definition of BONJ includes the presence of necrotic bone for more than 6 weeks in an area of the oral cavity normally covered by mucosa, prior or current bisphosphonate use, and no prior history of radiation to the head and neck.[1] The risks of BONJ increase with more frequent scheduling (ie, monthly) and prolonged durations of administration (ie, $>$ 2 years) of intravenous bisphosphonates, and the major risk factor for BONJ is dental extractions or procedures that expose bone during antiresorptive therapy. Principally, this led to the recommendation that, before initiating bisphosphonates, a dental evaluation and, if needed, dental work be completed before starting these drugs.[2] Small nonrandomized cohort studies suggest that the incidence of BONJ is decreased with dental screening before initiating intravenous (IV) bisphosphonates.[3,4] There is no evidence that routine dental health maintenance increases the risks of BONJ, and patients should be encouraged to have routine care during treatment with these drugs.

The precise mechanism(s) of BONJ or why it is confined to the jaw, predisposing risk factors other than dental extractions, optimal treatments, and more importantly, the short- and long-term outcomes and health-related quality of life of patients who develop BONJ are largely unknown.[5-7] Some, but not all, recent studies suggest that genetic polymorphisms in genes related to bone metabolism, collagen, or aromatase may predispose patients to BONJ.[8,9] As is true of other rare but serious complications of cancer treatment, health professionals tend to overestimate or underestimate the risks, depending on their specialty (eg, dentists or medical oncologists), general knowledge of BONJ, and anecdotal experience. In addition, recent small studies in patients seen in either dental or cancer clinics suggest that awareness and education about BONJ is lacking.[10,11]

Rathbone et al,[12] on behalf of the Adjuvant Zoledronic Acid to Reduce Recurrence (AZURE) trial investigators, have made an important contribution by providing the incidence and outcomes of BONJ in a prospective randomized controlled trial of zoledronic acid in more than 3,000 women with localized breast cancer receiving adjuvant systemic therapy and assessing the oral health-related quality of life in a small subset of them. Several aspects of the trial are noteworthy. The trial opened in 2003, which is the same year that BONJ was first described. In 2004, the protocol and consent was amended to exclude women with active dental issues or recent jaw surgery, consent was reaffirmed for all prior trial enrollees, educational materials were provided to all trial participants and investigators, and suspected cases of BONJ were reported as serious adverse events in real time to the trial coordinating center. These then triggered requests for additional information, and the final case determinations were adjudicated by the study team, which included an oral surgeon.

Thus to the extent possible, investigators and trial participants were made aware of the potential of BONJ. However, we do not know whether a standard approach to case ascertainment of BONJ was performed at every clinic visit for all women enrolled onto the trial. For example, in recently closed Cancer and Leukemia Group B (CALGB) trial 70604 (ClinicalTrials.gov trial number NCT00869206) trial participants were queried about dental problems, visits, and procedures they had had in the past 1 to 12 months, and the information was recorded in the monthly case report form. Without such a standard approach to case ascertainment, the potential bias of under- or over-reporting suspected cases of BONJ is possible.

The schedule of zoledronic acid in the AZURE trial was intensive, with one 4-mg dose administered every 3 to 4 weeks for 5 to 6 months, followed by one dose every 3 to 6 months for 46 months, or a total of 19 doses in 5 years. This schedule approximates the 24 once-per-month zoledronic acid doses typically used to treat women with breast cancer and skeletal metastases. It is interesting to note that, in the Austrian Breast Cancer Study Group (ABCSG) trial-12, in which more than 1,800 premenopausal women received goselerin and were randomly assigned to either tamoxifen or anastrozole with or without zoledronic acid, treatment with zoledronic acid reduced the risk of local recurrence, bone metastases, and distant metastases (overall hazard ratio, 0.68; 95% CI, 0.51 to 0.91; $P = .009$).[13] The schedule of zoledronic acid in the ABCSG trial was one 4-mg dose every 6 months for 3 years or a total of 6 doses, and there were no reports of BONJ (median follow-up, 62 months).

In the AZURE trial, the overall cumulative incidence of BONJ at 108 months was 2.1% (95% CI, 0.9% to 3.3%) and, extrapolating from Figure 1 of the article,[12] was about 1.1% at 36 months. This is

comparable with the cumulative estimated incidence of BONJ of 1.4% at 3 years in women with breast cancer receiving once-per-month zoledronic acid for skeletal metastases.[14] The 1.1% rate is about four-fold higher than that reported in a meta-analysis of randomized trials of less frequently scheduled zoledronic acid to mitigate bone loss in early-stage breast cancer, in which the incidence is about 0.25%.[15] More than 80% of the identified patients with BONJ had dental extractions before being diagnosed with BONJ, consistent with the range of 40% to 90% of dental extractions preceding BONJ.[16]

The outcome of 26 women with BONJ is provided in Table 3 of their article.[12] "Completely recovered" and "improving" were the outcomes for 35% and 19% of the BONJ population, respectively, whereas "recovered with sequela" and "present and unchanged" were the outcomes for 12% and 31%, respectively. It is unfortunate that precise definitions were not provided for these descriptors, nor were the details of the specific treatments for BONJ described. The optimal treatment of BONJ is not defined. In a recent review article, "healing" of BONJ associated with medical treatments, surgical debridement, and surgical flap and/or resection was 18%, 17%, and 46%, respectively,[6] but these were nonrandomized, retrospective, and cohort studies subject to patient selection and other biases.

Among the relevant questions to women with breast cancer receiving zoledronic acid or denosumab are "What are my chances of developing BONJ, and if I do, how does the disease and its treatment affect my life in the short- and long-term?" The answer to the first part of that question is clearly low—between 0.2% to 2%, depending on whether the treatment is intended to prevent/treat osteoporosis, prevent skeletal metastases in the context of a clinical trial, or treat skeletal metastases. The results of a quality-of-life component described by Rathbone et al[12] performed in a subset of trial participants does not address the quality of life in women who developed and live with BONJ; rather, at 5 years after random assignment, there were no differences in the domains of oral health-related quality of life in a small subset of women respondents randomly assigned to zoledronic acid or to a control arm using the Oral Health–Related Profile 14,[17] an instrument well-validated in noncancer populations.

These results may provide a modicum of reassurance that receiving zoledronic acid does not seem to be associated with a detectable impact on oral health–related quality of life 5 years down the road. However, the authors appropriately recognize that this one-time retrospective assessment of oral health–related quality of life limits our ability to make any definitive conclusions. There are few data assessing quality of life in women with BONJ. In a nonrandomized comparison of 42 women with metastatic breast cancer receiving IV bisphosphonates, quality of life as assessed by the Head and Neck Quality of Life Questionnaire–35 was statistically significantly worse in the domains of pain, swallowing, speech, social eating, social contact, and several others for those who developed BONJ.[18] Nearly 50% of women who developed BONJ in the AZURE trial were characterized as either "recovered with sequela" or "unchanged" at last follow-up. What happened to these women and how much impact and interference BONJ is having on their daily lives is unknown.

The results from two large cooperative trials using IV zoledronic acid—CALGB 70604 in more than 1,800 patients with metastatic breast cancer, prostate cancer, and multiple myeloma and a SWOG trial (ClinicalTrials.gov number NCT00127205) of more than 5,000 women with early-stage I-III breast cancers receiving adjuvant therapy comparing the oral bisphosphonates clodronate and ibandronate with IV zoledronic acid—should contribute additional information. CALGB 70604 is designed to determine whether once-every-3-months IV zoledronic acid is not inferior to the standard once-per-month schedule (8 *v* 24 doses) with a primary end point of the incidence of skeletal-related events and secondary end points of the incidences of BONJ, renal dysfunction, and pharmacogenomics using whole-genome analysis. In the SWOG trial, the oral bisphosphonates are administered daily for 3 years with an intense schedule of zoledronic acid of one 4-mg dose every month for 6 months followed by one 4-mg dose every 3 months for 30 months, or a total of 16 doses in 3 years. The primary end points are disease-free survival, overall survival, and adverse events. Results are expected in 2014 for the CALGB trial and 2015 for the SWOG trial.

The incidence of BONJ is likely decreasing since it was first reported in 2003 as a result of increasing awareness and a more precise definition of the disease, disseminating recommendations for dental screening, and limiting the schedule and duration of monthly treatments. When IV zoledronic acid is used for cancer treatment–related bone loss, the incidence of BONJ is low (about 0.25%) and lower still with use of oral bisphosphonates. Likewise, the 1% to 1.5% incidence of BONJ with 24 once-per-month zoledronic acid treatments in treating skeletal metastases in women with breast cancer is probably acceptable in most cases. If the results of CALGB 70604 indeed show that less frequent dosing of zoledronic acid is not inferior to the standard monthly dosing, then this will also likely lower the incidence of BONJ.

The use IV zoledronic acid to improve patient outcomes is a work in progress, and the results from the SWOG trial should provide additional data. Overall, the AZURE trial results[19] showed that IV zoledronic acid on an intensive schedule did not improve disease-free survival or overall survival, and therefore the 2% total cumulative incidence of BONJ, although low, is clearly not acceptable. Whether there is a subpopulation of women with early-stage breast cancer as has been proposed—premenopausal receiving ovarian suppression[13] or postmenopausal women[19,20,21]—in which the therapeutic ratio favors using adjuvant zoledronic acid or clodronate vis-à-vis BONJ and other adverse effects remains to be verified in subsequent trials. Finally, the incidence of osteonecrosis of the jaw related to monthly denosumab is slightly higher than that reported for zoledronic acid when used in patients with skeletal metastases.[22] Phase III trials are addressing the role of denosumab to improve clinical outcomes in women with early-stage breast cancer.

AUTHOR'S DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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