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Focus On

Current status of adjuvant bisphosphonates in operable breast cancer

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Abstract Bisphosphonates offer a potentially effective adjuvant therapy to reduce recurrence of bone metastases in breast cancer patients. Clinical trials are at the early stage, but initial results have shown promise. There are three published adjuvant trials of oral clodronate, and one trial each of pamidronate and zoledronic acid. Observed complications so far include osteonecrosis of the jaw or maxilla because bisphosphonates inhibit bone turnover, as well as renal toxicity. Thus, care needs to be taken with dosage and duration of treatment and patients carefully managed.

Keywords: Adjuvant therapy; Bisphoshonates; Bone metastases

Predicting bone metastases

The ability to predict which patients are likely to develop bone metastases has received increasing attention with the development of bone active medications, which hold the possibility of preventing harmful skeletal events and perhaps bone metastases.

Studies of bone marrow aspirations in patients presenting with primary breast cancer do suggest poorer prognosis in those patients with detectable cancer cells but there is insufficient evidence to support routine use [1]. However, the presence of malignant cells within the marrow at the time of presentation does not necessarily mean that the first site of recurrence will be within bone. This is similar to the presence of axillary metastases that are predictive of relapse at some site but not necessarily the axilla.

Bone markers such as N- or C-telopeptide have not been helpful in predicting bone disease, although they can be helpful in managing bone pain where rising levels of N-telopeptide in the serum and urine may lead to adjustment of dosages of bisphophonates to reduce the bone marker levels, sometimes relieving bone pain [2].

Other markers which have been assessed for early diagnosis include bone sialoprotein [3], PINP (procollagen I N-terminal propeptide) [4] and serum alkaline phosphatase levels. Bone sialoprotein may be a candidate marker but confirmatory studies are required. In the case of PINP, elevation and subsequent drop in the levels of this marker of bone turnover may predict in some patients for development of bone metastases and inhibition of these metastases by clodronate but it may not be sufficiently frequently expressed to be used as a routine marker of prediction.

Many studies are ongoing using DNA microarrays and genetic profiling looking for patterns predictive of bone metastases [5]. These are not sufficiently developed to be used in the clinic.

Incidence of bone metastases

Coleman and Rubens [6] reported in 1987 that in 587 patients dying of breast cancer, 69% had radiological evidence of bone metastases before

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death compared to lung and liver metastases (27% each). In this same report describing 2240 patients presenting with breast cancer and followed for a median of 5 years, 47% of those relapsing at distant sites relapsed in bone. It is likely that with radiological techniques of magnetic resonance imaging this proportion would be found to be higher today.

National Surgical Adjuvant Breast and Bowel Project (NSABP) data also show that bone metastases account for the highest proportion of first sites of distant relapse in breast cancer patients. Nearly half of the patients who developed distant metastases did so in bone either as the sole site of recurrence or simultaneously with other sites of disease. The annual rate of bone metastasis development was higher in node-positive patients (approximately 2% per annum) than in node-negative ones (approximately 1% per annum) and higher in ER-positive patients than in ER-negative ones [7]. Recurrence rates in bone in current NSABP trials seem to be lower than at the time of the above NSABP report, probably due to a reduction in all sites of recurrence because of more effective therapies.

Adjuvant trials

The antitumor effects of bisphosphonates observed in preclinical studies have not been unequivocally reproduced in the clinical setting to date. Data from clinical trials of adjuvant bisphosphonate therapy suggest that their use in this setting may be beneficial, but these data have been inconsistent across trials. There are three published adjuvant trials of oral clodronate, and one trial each of pamidronate and zoledronic acid.

Clodronate

In a single-center trial of 302 women with primary breast cancer, patients received either postoperative treatment with oral clodronate (1600 mg) for 2 years or no treatment [8]. After a 3-year follow-up, patients in the adjuvant clodronate group had a lower incidence of bone metastases than those in the untreated control group ($P = 0.044$). There was a longer overall survival time in the clodronate group ($P < 0.002$).

A 10-year (103 months $\pm$ 12 months) follow-up study of 290 of the original patients found that the significantly longer disease-free survival was not maintained, but that clodronate still improved overall survival ($P = 0.01$); 79.6% of clodronate-treated patients survived compared with 59.3% of patients who received placebo [9].

Results obtained from a randomized, placebo-controlled clinical trial of adjuvant clodronate suggest that it may increase bone metastasis-free survival for patients with breast cancer. Adjuvant oral clodronate was assessed in a 2-year, randomized, placebo-controlled trial in 1069 women with primary operable breast cancer [10]. Clodronate resulted in a significantly lower incidence of bone metastasis, by 45% during the first two years ($P = 0.031$) and by 31% during the 5-year study period ($P = 0.043$) compared with placebo. There was also a significantly longer overall survival time compared with placebo ($P = 0.047$). After a 10.5-year follow-up, oral clodronate was still found to significantly improve overall survival ($P = 0.048$) [11].

In contrast, a third trial did not find a benefit for the use of adjuvant oral clodronate in patients with node-positive breast cancer [12]. In a randomized, open label trial of clodronate given for 3 years, the incidence of bone metastases at five years was higher in the clodronate-treated patients than in patients in the control arm. Furthermore, both overall and disease-free survival times were significantly shorter in women treated with clodronate compared with those who received placebo. After a 10-year follow-up, no significant difference in survival was seen between patients who received clodronate and those who received placebo, but disease-free survival was still shorter in the clodronate group [13]. The results of this trial are concerning, but they are most likely explained by a randomization bias. Significantly more patients with estrogen receptor-negative and progesterone receptor-negative breast cancer were randomized to the clodronate group.

Pamidronate

Kokufu *et al*. [14] assessed the effects of pamidronate in a small ($n = 90$), non-randomized study of patients with high-risk breast cancer (four or more positive nodes). With a median follow-up of 5.4 years, patients who received adjuvant pamidronate had a lower incidence of bone metastases ($P = 0.008$) and a higher metastasis-free survival ($P = 0.035$) than controls. These findings require confirmation.

Zoledronic acid

Adjuvant zoledronic acid was studied in a randomized, open-label trial of 40 patients with recurrent solid tumors who did not present with bone metastases at baseline [15]. After 12 months, significantly more patients in the zoledronic acid group were free from bone metastases than patients in the control group (60% vs. 10%; $P < 0.0005$). This difference remained significant at 18 months (20% vs. 5% for placebo; $P = 0.0002$).

Ongoing adjuvant trials

A number of well-designed, randomized, trials of bisphosphonate therapy for early-stage breast

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cancer are currently under way. NSABP B-34, assessing oral clodronate versus placebo, may provide further evidence for efficacy in the adjuvant therapy of breast cancer. Because of the low recurrence rates seen in this predominantly Stage 1 trial, results are not expected until 2009. Trials are also currently evaluating the relative roles of adjuvant intravenous (i.v.) zoledronic acid, oral clodronate and oral ibandronate. The S0307 trial is designed to assess the efficacy of bisphosphonates in reducing the incidence of bone metastases. It is a 4-year, joint SWOG/Intergroup/NSABP trial in 6000 women with breast cancer. The trial started at the end of 2005 and is due to end in 2015. After 3 years of treatment, patients will be followed up for an additional 3 years. Enrolled patients will randomly receive one of three adjuvant bisphosphonate regimens, in addition to standard systemic therapy [16]. The trial will enroll female patients with histologically confirmed stage I, II, or III non-metastatic breast cancer who are receiving standard adjuvant therapy. Entry criteria are standard, but a new feature in this trial is a requirement for a pretrial dental examination for identification of periodontal disease and exposed bone; this is in an effort to reduce any potential risk factors for osteonecrosis of the jaw or maxilla.

Some problems

Bone re-modelling is a normal repair mechanism. Basic multicellular units (bone resorption bays) are formed in order to repair areas of effete or damaged bone. Bisphosphonates are potent inhibitors of bone turnover and therefore it is not surprising that the quality of bone formed may differ from normal bone. The more potent aminobisphosphonates may be particularly problematic in this regard when they are used over a period of several years in the adjuvant setting of women with breast cancer who have normal bone. In experimental animals given high doses of bisphosphonate therapy, there occurs an accumulation of micro-fractures with consequent diminution of bone strength. This has been well discussed by Ott (2005) [17].

Recently, 63 cases of osteonecrosis of the maxilla or mandible were reported in patients receiving i.v. pamidronate and zoledronate (55 patients) and oral risedronate and alendronate (8 patients) [18]. This is a painful, poorly healing or non-healing necrosis of the tooth socket following dental extraction leading to osteonecrosis of the mandible or maxilla. It is a difficult condition to treat, often requiring excision of bone. Bisphosphonates have potential for interference with bone repair. Their half-life is several years and it is likely that all bisphosphonates might cause this toxicity although it is only occasionally seen with oral clodronate. Increased fractures have been observed in Paget's disease with etidronate [19] and a case report of osteopetrosis in a child on i.v. pamidronate which also led to increased fractures [20] indicates that these agents must be used with care, using the lowest dose and frequency which is efficacious for the end-point sought. Their routine use for months (and sometimes years) on end with minimum supervision is poor practice.

Renal toxicity can be another problem, especially with i.v. bisphosphonates. A retrospective analysis of 57 patients with bone metastases from various cancers who were treated with i.v. bisphosphonates for over 24 months (most switching from i.v. pamidronate to i.v. zoledronate given every 3–4 weeks) was conducted to assess long-term renal safety [21]. All patients studied had a normal baseline serum creatinine; 12.2% experienced increased serum creatinine levels, 3 patients (5%) suffered osteonecrosis of the jaw. The main message here is that all patients receiving i.v. bisphosphonates should have a serum creatinine drawn prior to administration as well as an oral examination at each visit. Patients on oral bisphosphonates should have a creatinine drawn and an oral examination at each 3–6 monthly visit.

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