Adjuvant Bisphosphonates in Breast Cancer Treatment

Michael Knauer · Beat Thürlimann

Breast Center St. Gallen, Switzerland

Keywords

Breast neoplasms · Adjuvant therapy · Bisphosphonates · Bone health

Summary

Several solid tumors like breast cancer tend to spread to the bone, where the microenvironment is especially receptive to the tumor by special interactions between bone cells and tumor cells. Bone metastases often lead to skeletal-related events with significant morbidity and mortality. The therapy of bone metastases and osteoporosis with bisphosphonates (BPs) has been established many years ago as a standard treatment. In the adjuvant setting, cancer treatment-induced bone loss is a frequent cause of morbidity, and prevention and treatment of this condition with BPs and the monoclonal antibody denosumab are also well established. Besides postmenopausal patients, several studies including 2 larger studies by the Austrian Breast and Colorectal Cancer Study Group (ABCSG) and the Cancer and Leukemia Group B (CALGB) have shown an increase in bone mineral density in premenopausal women. BPs as anticancer treatment are, however, still controversial because several studies yielded conflicting results, with beneficial effects only in subgroups of patients. The publication of the latest Oxford overview of prospective trials is being awaited; at the presentation of the results, a 34% relative reduction of bone metastasis and a 17% improvement in overall survival was demonstrated in the subgroup of postmenopausal patients. These results will likely lead to an incorporation of the use of BPs into routine adjuvant breast cancer treatment.

Introduction

Bisphosphonates (BPs) as structural analogs of pyrophosphates are ingested by osteoclasts after binding to the bone. As a result, osteoclast-mediated bone resorption is inhibited, leading to an increase in bone mineral density (BMD) [1]. Many solid tumors including breast cancer have a particular propensity for the bone, whereas the microenvironment is highly receptive to the tumor by special interactions between bone cells and tumor cells [2]. Bone metastases often lead to unpleasant skeletal-related events (SREs), i.e. osteolytic lesions and pathologic fractures, hypercalcemia of malignancy or the requirement for surgery or radiotherapy to the bone [3]. BPs are classified into 2 groups of agents: the less potent non-nitrogen-containing BPs like etidronate and clodronate and the newer, nitrogen-containing BPs like pamidronate, alendronate, ibandronate or zoledronate, for example. In the metastatic setting, BPs have been used for more than 20 years for the treatment of hypercalcemia and bone pain, and for the prevention of potentially fatal SREs [4]. More recently attention has been attracted to an antitumor activity potential of BPs in the adjuvant setting, which is the focus of this review.

Adjuvant BPs for the Prevention and Treatment of Therapy-Associated Bone Loss

Adjuvant breast cancer therapies like anti-estrogen treatment and chemotherapies affecting ovarian function frequently result in an increase of the naturally occurring loss of BMD. The resulting osteoporosis is associated with significant morbidity and even mortality. Because nearly one-third of new breast cancer diagnoses occur in premenopausal women with long life expectancy after the primary oncological therapy, treatment-induced osteoporosis is of special interest in these patients. Premature ovarian failure as a result of endocrine therapy, chemotherapy or surgery mediates the risk of

Table 1. Studies of adjuvant ZA in breast cancer included in the 2013 systematic review [16]

Study (year)	Intervention	Patients, n	Follow-up, months
AZURE trial (2011)	ZA vs. observation	1,681 1,678	59,3 58,6
ABCSG-12 trial (2011)	ZA vs. observation	900 903	84 84
ZO-FAST (2011)	upfront ZA vs. delayed ZA	532 533	54 54
Z-FAST trial (2011)	upfront ZA vs. delayed ZA	300 300	61 61
N03CC trial (2009)	upfront ZA vs. delayed ZA	274 277	24 24
EZO-FAST trial (2009)	upfront ZA vs. delayed ZA	263 264	36 36
HOBEO trial (2011)	ZA vs. observation	154 305	NR
KCSG-BR06-01 trial (2011)	ZA vs. observation	57 59	NR
ProBone trial (2011)	ZA vs. placebo	40 41	NR
Takahashi et al. (2011)	upfront ZA vs. delayed ZA	97 97	12 12
Aft et al. (2010)	ZA vs. observation	60 59	61.9 61.9
Hershman et al. (2010)	ZA vs. placebo	50 53	24 24
Safra et al. (2011)	ZA vs. observation	47 43	41.4 41.4
Leal et al. (2010)	ZA vs. observation	36 32	96 96
Swenson et al. (2010)	ZA vs. physical activity	33 29	12 12

ZA = Zoledronic acid, NR = not reported.

long-term bone-related toxicity. Although no prospective studies exist that formally compare naturally occurring loss of BMD to cancer treatment-induced bone loss (CTIBL), this has been described in studies of tamoxifen and gonadotropin-releasing hormone (GnRH) analogs in premenopausal patients [5–8]. After adjuvant chemotherapy, the percentage of BMD decrease in the first year ranges between 3 and 8% [9]. In postmenopausal breast cancer patients, the natural BMD decrease is aggravated especially when aromatase inhibitors are being used.

BPs and the receptor activator of NF- κ B ligand (RANKL)-inhibiting monoclonal antibody denosumab are widely used for the prevention and treatment of CTIBL, if a T-score of less than -2.5 is observed. 2 larger prospective trials have been conducted in premenopausal patients to study the effects of zoledronic acid (ZA) on BMD. In the Austrian Breast and Colorectal Cancer Study Group (ABCSG)-12 study, a total of 1,803 patients received either tamoxifen or anastrozole with or without ZA in addition to the GnRH analog goserelin [8]. Patients receiving 4 mg ZA every 6 months for 3 years experienced no significant CTIBL as compared to patients on placebo, who showed a reduction of

14% in BMD or a T-score reduction of -1.4 . In the Cancer and Leukemia Group B (CALGB) 79809 study, 166 premenopausal women aged > 40 years were randomized to ZA every 3 months or placebo for 2 years. After 1 year of follow-up, the patients on ZA showed an increase in BMD by 1.2% versus a loss of 6.7% in patients receiving placebo [9]. In postmenopausal breast cancer patients, BPs and denosumab are well established for the prevention of CTIBL in addition to treatment of osteoporosis.

BPs as Anticancer Agents

The role of osteoclast-inhibiting drugs such as denosumab or BPs regarding their potential to improve breast cancer outcome by direct antitumor effects is heavily debated due to conflicting study results. Preclinical and early clinical data suggest that these agents could interrupt the so-called ‘vicious cycle’ of bone destruction. The receptor activator of NF- κ B (RANK) signaling pathway plays an important role in the interaction between tumor cells, osteoblasts, and osteoclasts, as well as several growth factors like platelet-derived growth factor (PDGF),

transforming growth factor (TGF)- β , insulin-like growth factor (IGF), and fibroblast growth factor (FGF), and interleukin (IL)-6 and IL-8, influencing bone structure and mass [10]. Antitumor effects of BPs probably include antiangiogenic, anti-proliferative, and pro-apoptotic effects, reducing circulating tumor cells and bone marrow micrometastases [11–13].

The oncologic benefit of BPs in early breast cancer is, however, still controversial. Many prospective studies have been performed and several systematic reviews and meta-analyses have been published [14–16]. Hypotheses from early BP trials include that antitumor effects are mainly due to a reduction in bone metastases and that distant recurrence is predominantly reduced as compared to local or contralateral recurrence. Even these meta-analyses did not come to similar conclusions over the last few years. In the first systematic review by Mauri et al. in 2010 [14], ZA was not associated with a significant reduction in bone metastases or death. In the latest peer-reviewed meta-analysis by Valachis et al. from 2013 [16] including 15 eligible trials, a significant improvement for overall survival and fracture rates but not for disease-free survival or incidence of bone metastasis was shown for the overall study population (table 1), a finding that cannot be interpreted easily.

Early Breast Cancer Trialists' Collaborative Group Meta-Analysis of Adjuvant BPs

Coleman et al. [17] presented the results of a systematic review by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) during the last San Antonio Breast Cancer Symposium. This pooled meta-analysis of individual patient data comprised nearly 18,000 patients from 22 prospective trials. As a result of this presentation, many institutions reconsidered their policy of using adjuvant BPs in early breast cancer. Because of previously shown conflicting study results and since the full publication of the EBCTCG meta-analysis still has to be awaited, no general recommendations are made for the implementation of BPs into clinical routine. The German S3 guidelines from 2012, for example, do not comment on adjuvant BP use. However, the more recent yearly update from March 2014 by the 'Arbeitsgemeinschaft Gynäkologische Onkologie' (AGO) supports the use of adjuvant oral clodronate or aminobisphosphonates for postmenopausal patients with a grade A recommendation of this level 1a evidence [18]. The 2014 version of the American National Comprehensive Cancer Network (NCCN) guidelines, on the other hand, does not give a statement regarding the use of BPs in the adjuvant setting [19].

Across all prospective trials there is a lack of consistent benefit for oncologic outcome measures. Furthermore, in some trials, only subgroups of patients achieved an improvement in outcome, e.g. only the postmenopausal patients

within the Adjuvant Zoledronic Acid to Reduce Recurrence (AZURE) trial [20]; so it remains somewhat unclear for which indications adjuvant BPs should or could be used. This is the reason why in the recent EBCTCG meta-analysis a wide spectrum of pre-planned subgroup analyses were performed, considering all their associated statistical difficulties. In all 17,709 patients from 22 studies, no significant reduction was observed for all recurrences in the entire patient population; however, a statistically significant but clinically probably irrelevant 1.4% ($p = 0.03$) absolute reduction of distant recurrences at the 10-year follow-up was shown. In contrast to non-bone metastases where no significant effect of BPs was found, the main improvement (1.5% absolute gain; $p < 0.001$) was observed for bone metastases. Regarding local and contralateral recurrence, no effect was seen for these outcome measures, which could be an indirect sign that BPs would not work as a medical prevention strategy. Focusing on the relevant subgroup of 11,036 postmenopausal women including patients with induced menopause and 1,564 events, there was a clear 3.5% benefit ($p < 0.001$) regarding distant recurrence, which was obviously restricted to bone recurrences (2.9% absolute and 34% relative benefit; $p < 0.001$). Patients with other than bone metastases certainly did not benefit from this intervention; however, no adverse effect was observed in these women by using BPs. The effect sizes on bone metastases in postmenopausal women were similar regardless of whether clodronate (hazard ratio (HR) 0.57) or an aminobisphosphonate (HR 0.70) was used. Furthermore, no influence of the estrogen receptor (ER) status, the nodal status, or the chemotherapy was shown in the presentation. Regarding breast cancer-specific mortality, a relative reduction of 17% led to an absolute benefit of 3.1% ($p < 0.001$) and 2.3% improvement of overall survival, respectively, at 10 years. However, the EBCTCG meta-analysis and the conclusions drawn in favor of BP use as standard with antineoplastic intention have been criticized, e.g. at the last European Breast Cancer Conference (EBCC) in 2014, during an arena debate. When the manuscript of this EBCTCG meta-analysis will be finally published, these results will probably be incorporated in several treatment recommendations and guidelines. This has the potential for a further small but significant improvement in the therapy of early breast cancer, with the size of the treatment effect being similar to the advantage gained from aromatase inhibitors over tamoxifen or taxanes over anthracycline-based chemotherapy. We are anxiously looking forward to the next St. Gallen Consensus Conference in 2015 in Vienna where the panelists will have to deal with the ongoing controversy.

Disclosure Statement

The authors have no disclosures relevant to this manuscript.

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