Cancer Treatment Reviews 40 (2014) 476–484

Contents lists available at SciVerse ScienceDirect

Cancer Treatment Reviews

journal homepage: www.elsevierhealth.com/journals/ctrv

General and Supportive Care

Role of bisphosphonates in postmenopausal women with breast cancer

Michael Gnant *

Department of Surgery, Comprehensive Cancer Center, Medical University of Vienna, Austria

ARTICLE INFO

Article history:
Received 24 April 2013
Received in revised form 2 July 2013
Accepted 8 July 2013

Keywords:
Adjuvant therapy
Anticancer
Bisphosphonate
Bone mineral density
Breast cancer
Clodronate
Survival
Zoledronic acid

ABSTRACT

Data suggest that bisphosphonates protect bone health and may have anticancer activity in postmenopausal women during adjuvant breast cancer therapy. However, key questions remain surrounding the role of adjuvant bisphosphonates in breast cancer, including patient populations deriving benefit, timing/scheduling of therapy, and specific clinical benefits. PubMed, Embase, and San Antonio Breast Cancer Symposium databases provide study results that address these issues in postmenopausal women. Review of these data would aid physicians in providing optimal management of breast cancer in postmenopausal women. For example, recent data reinforce use of intravenous bisphosphonates concurrently with adjuvant endocrine therapy to ameliorate bone loss in recently postmenopausal or osteopenic postmenopausal women with early breast cancer. In contrast, clinical data for oral bisphosphonates have not provided support for using anti-osteoporosis doses in this setting, and the optimal dose is unclear. Additionally, current clinical data show improvements in disease outcomes with bisphosphonates in many studies, although not in all patient subsets. Strong support for the potential adjuvant anticancer benefits from bisphosphonates has been demonstrated in women with established menopause (i.e., very low circulating estrogen levels). Initiating bisphosphonates early and concomitantly with adjuvant therapy generally provided the greatest benefits. However, questions remain such as schedule of treatment and relative potency among the intravenous bisphosphonates and elucidation of the role of oral bisphosphonates, as well as ongoing studies that might provide clarification. This review addresses these controversies in the context of translational research, which may provide the rationale for ongoing studies and evolving treatment paradigms in this area.

Introduction

Preserving and/or restoring bone health is an important component of modern breast cancer (BC) management. Although the overall incidence of BC has been in decline since peaking in 1999, the risk of developing BC increases with age [1,2]. Postmenopausal women also lose bone mineral density (BMD) as they age, and treatments for BC can lead to further decreased BMD as an unwanted side effect of effective antineoplastic therapies due to estrogen depletion, [3] thereby increasing the risk of fragility fractures.

Bone remains in a dynamic state throughout life, continually being resorbed by osteoclasts and reformed by osteoblasts in a coordinated fashion that maintains the structural integrity of the skeleton [4]. This process of bone turnover is affected by numerous factors such as estrogen (associated with increased bone mass and prevention of bone loss) and receptor activator of nuclear factor kappa-B (RANK) ligand (key mediator of osteoclast differentiation) [3]. In postmenopausal women, decreased estrogen levels and osteoblast activity lead to bone loss, which can progress to osteopenia or osteoporosis [5]. Treatments for early BC in postmenopausal women can lead to additional bone loss, which renders more patients osteopenic or osteoporotic [6]. Moreover, the development of bone metastases further dysregulates bone turnover by affecting localized bone resorption or formation [6].

Bisphosphonates inhibit bone resorption at sites of active bone metabolism, thereby restricting bone destruction but allowing bone growth [7]. Thus, bisphosphonates preserve BMD in women with osteoporosis or receiving BC treatments that lead to bone loss, as well as reduce the risks of skeletal morbidity in patients with bone metastases from BC [6,8]. Bisphosphonates, by reducing the production of osteolysis-derived growth factors, may also render the bone microenvironment unsupportive of tumor cell survival, thereby reducing the incidence of BC recurrence [9]. Therefore, bisphosphonates may have an expanding role in the management of BC.

This review examines recent data investigating bisphosphonate use in postmenopausal women with BC, with a critical assessment

* Address: Department of Surgery, Comprehensive Cancer Center, Medical University of Vienna, Währinger Gürtel 18-20, A-1090 Vienna, Austria. Tel.: +43 1 40400 5646; fax: +43 1 40400 6807.
E-mail address: michael.gnant@meduniwien.ac.at

0305-7372/$ - see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.ctrv.2013.07.003

of current unresolved issues and how they are being addressed by ongoing preclinical and clinical research.

Search strategy and selection criteria

The PubMed database was searched (from January 2008 to date) for recent trials published in English evaluating a bisphosphonate in postmenopausal women with BC, using the terms "postmenopausal," "breast cancer," and "bisphosphonate." The Embase database was also searched during the same timeframe using the terms "postmenopausal" and "breast cancer" with either "zoledronic acid," "risedronate," "ibandronate," "clodronate," or "alendronate." Searches in both databases were limited to clinical trials, randomized controlled trials, and meta-analyses. PubMed retrieved a total of 27 publications for evaluation, with 18 publications deemed relevant. Embase retrieved a total of 51 publications for evaluation, with 13 relevant publications (2 not found in PubMed). Overall, the results from 20 publications are reviewed.

Abstracts from the 2011 and the 2012 San Antonio Breast Cancer Symposium were searched using the terms "bisphosphonate," "zoledronic acid," "risedronate," "ibandronate," "clodronate," or "alendronate" to identify bisphosphonate trials in postmenopausal women with BC. A total of 28 abstracts were retrieved for evaluation from 2011, with 6 relevant abstracts. A second literature search immediately before submission showed that 3 of these abstracts were subsequently published (2 as a single journal article). A total of 17 abstracts were retrieved for evaluation from 2012, with 4 relevant abstracts.

Of the 33 relevant publications (not counting the 2 publications noted above) that presented data on bisphosphonate use in postmenopausal women with BC, 24 were in patients with early BC receiving adjuvant therapy. The relevant publications were in 2 broad areas – BMD preservation during BC treatment and anticancer benefits of bisphosphonates. Zoledronic acid (ZOL) was investigated most frequently (18 publications), followed by risedronate (5 publications), ibandronate (2 publications), and clodronate and alendronate (1 publication each).

Bisphosphonates for bone health in postmenopausal women with early breast cancer

In early BC, adjuvant therapy (endocrine and chemotherapy) may lead to substantial bone loss that may result in osteopenia or osteoporosis, which can increase fracture risk [8]. Aromatase inhibitors (AIs), in particular, further reduce estrogen levels in postmenopausal women, which can accelerate bone loss, [10] thereby necessitating monitoring of BMD and/or fracture risk [10]. This is of particular importance because 31% of BC patients at the time of diagnosis had pre-existing osteopenia in 1 study [11]. It has been demonstrated that these patients, in particular, are at considerable risk to be "pushed" into osteoporosis and/or suffer from clinical fractures during AI treatment [12]. The majority of recent adjuvant BC studies evaluated bisphosphonates to ameliorate bone loss and determine optimal timing of treatment initiation (Table 1) [11,13–27].

Recent clinical studies

There have been several recent adjuvant studies evaluating oral bisphosphonates for bone health in postmenopausal patients with BC. Risedronate (35 mg/week) reduced the rate of BMD loss during AI therapy in patients with chemotherapy-induced menopause (mean ~3 years) [13] and improved BMD during adjuvant therapy in postmenopausal patients at varying risks for fragility fractures [14,15]. A preplanned subanalysis on hip structure showed that although risedronate improved several hip structure parameters regardless of AI use, the greatest improvement was observed in patients who did not receive an AI [28,29]. The use of an AI may therefore lead to changes in bone structure beyond BMD, for which anti-osteoporosis doses of bisphosphonates may not totally compensate. In this study, fracture rates were too low to analyze for clinical benefit. Alendronate (70 mg/week) ameliorated BMD loss compared with placebo when initiated within 3 months of tamoxifen discontinuation in postmenopausal women [16]. Tamoxifen can increase BMD in the lumbar spine of postmenopausal women, an effect that may be reversed upon discontinuing therapy [30,31]. However, as the use of AIs increases, especially with switching between tamoxifen and AI therapy occurring more often, the practical guidance from this study may be applicable to only a small percentage of patients. Oral ibandronate (150 mg/month) provided a greater proportion of patients with increased BMD at the lumbar spine and total hip versus placebo in 131 postmenopausal women with early BC who received anastrozole 1 mg/day [17]. Fracture rates in this study were also too low to analyze for clinical benefit, although the study does provide support for BMD improvement with an oral bisphosphonate in this setting.

One of the key issues that may contribute to the discordant clinical benefits observed with oral bisphosphonates is compliance. In the single risedronate study reporting compliance ($\geqslant$80% of medication taken), only 65% of patients in the risedronate group were compliant at the end of the study (year 2) [13]. In contrast, the ibandronate study reported more than 90% of patients taking all of their monthly doses of ibandronate after 2 years [17].

Among the intravenous bisphosphonates, recent results have been published only for ZOL in the adjuvant setting for postmenopausal women with BC [11,18–26]. In all studies, ZOL (typically at 4 mg every 6 months), initiated concurrently with systemic adjuvant therapy, increased BMD from baseline at the lumbar spine, femoral neck, and total hip by the first time point (~12 months). Increases in BMD were observed even if patients had osteopenia or osteoporosis at baseline. Several studies delayed the addition of ZOL to adjuvant therapy (in the control arms) until a patient's BMD T-score was below −2.0 or a fracture occurred [11,20–22,24,25]. This patient population generally had mean BMD decreases at all sites and, in 1 study, were more likely to have a clinically relevant 5% decline in BMD from baseline at 1 year at all sites compared with the immediate-ZOL group ($P \leqslant .0057$ for all) [20].

Interestingly, in 1 small study among postmenopausal women who did not receive ZOL, BMD loss at the lumbar spine was greatest among women who had entered menopause within 1 year of adjuvant treatment initiation compared with those who were more than 1 year postmenopausal ($P \leqslant .021$ at 12 and 24 months) [18]. These results are supported by a larger study wherein there was a more rapid BMD loss during letrozole therapy among the recently postmenopausal women compared with established postmenopausal women; however, the upfront addition of ZOL prevented this BMD loss [11].

There was 1 meta-analysis of studies reporting fracture data, which showed that bisphosphonates did not significantly reduce fracture risk compared with placebo or no treatment in the postmenopausal subgroup [27] (Table 1) [11,13–27]. However, the analysis was not stratified by the individual bisphosphonates, and not all bisphosphonates have the same activity for preventing bone loss and fractures during cancer therapy [8].

Consideration should also be given to premenopausal women who are rendered postmenopausal by BC treatments. In 1 study ($N = 73$), patients who experienced amenorrhea had an 8- to 19-fold increase in percent BMD loss compared with patients who remained menstruating at 5 years following chemotherapy [32]. Clodronate (1600 mg/day for 3 years) was able to ameliorate bone loss at the lumbar spine but not the femoral neck in this pa-