Clinical Oncology 25 (2013) 135–145

Contents lists available at SciVerse ScienceDirect

Clinical Oncology

journal homepage: www.clinicaloncologyonline.net

Overview

Bisphosphonates in the Adjuvant Treatment of Breast Cancer

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Received 19 September 2012; accepted 26 October 2012

Abstract

Bisphosphonates, as potent inhibitors of osteoclast-mediated bone resorption, significantly reduce the risk of skeletal complications in metastatic bone disease and also prevent cancer treatment-induced bone loss (CTIBL). However, more recently, there has been increasing data indicating that bisphosphonates exhibit anti-tumour activity, possibly via both indirect and direct effects, and can potentially modify the metastatic disease process providing more than just supportive care. The evidence from previous studies of an anti-tumour effect of bisphosphonates was inconclusive, with conflicting evidence from adjuvant oral clodronate trials. However, more recent trials using zoledronic acid have shown benefits in terms of disease-free and overall survival outcomes in certain subgroups, most evidently in older premenopausal women with hormone-sensitive disease treated with ovarian suppression, and in women in established menopause at trial entry. In the adjuvant setting, the use of bisphosphonates has also been focused on the prevention and treatment of CTIBL and recent guidelines have defined treatment strategies for CTIBL. The role of bisphosphonates in CTIBL in early breast cancer is well defined. There have been mixed results from large adjuvant metastasis-prevention studies of bisphosphonates, but there are strong signals from large subgroups analyses of randomised phase III trials suggesting significant anti-tumour beneficial effects in specific patient populations.

Key words: Adjuvant; anti-tumour activity; bisphosphonates; breast cancer; clodronate; zoledronic acid

Statement of Search Strategies Used and Sources of Information

Literature searches using PubMed, together with supplemental evidence from major international conference abstracts and presentations were used to identify relevant publications.

Introduction

In metastatic breast cancer, bone represents the first site of metastasis in about 50% of patients. Metastatic bone disease results from complex interactions between tumour cells and bone cells in the bone microenvironment. The normally balanced coupled process of osteoclastic bone resorption and osteoblastic bone formation is disrupted by growth factor and cytokine production by tumour cells leading to accelerated osteolysis, the hallmark of cancer-induced bone disease. Resultant skeletal-related events, such as hypercalcaemia, bone pain, pathological fracture and spinal cord compression, lead to devastating sequelae. Bisphosphonates, as potent inhibitors of osteoclast-mediated bone resorption, are firmly established in this treatment setting and significantly reduce the risk of skeletal complications from breast cancer [1].

However, data suggest that bisphosphonates may provide more than supportive care only and have the potential to modify disease course by disrupting the metastatic process. By modifying the bone microenvironment and rendering it less fertile for metastatic tumour growth, and with increasing evidence of a potential direct anti-tumour effect, the use of bisphosphonates in the adjuvant setting represents an exciting clinical strategy that has been investigated to prevent breast cancer recurrence.

It is also clear that adjuvant breast cancer treatments can have longer-term deleterious effects on bone health.

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0936-6555/$36.00
http://dx.doi.org/10.1016/j.clon.2012.10.010

Important strategies using bisphosphonates to prevent and treat cancer treatment-induced bone loss (CTIBL) have been developed. Adjuvant bone protection studies of zoledronic acid (ZOL) have clearly shown effective prevention of aromatase inhibitor-induced bone loss (AIBL) and have additionally provided further supportive evidence of an anti-tumour effect.

This overview details the current evidence of the use of bisphosphonates in the adjuvant setting, both in terms of the prevention of CTIBL and metastasis prevention. The potential efficacy of bisphosphonates in the prevention of disease recurrence has been investigated in a clinical trial programme of several large phase III trials, approximating 22 000 patients, and recently reported and published results and subsequent controversies will be highlighted.

Pathophysiology of Bone Metastases

The normal healthy steady-state remodelling process is destroyed in the presence of tumour cells in bone through the secretion of tumour cell-derived growth factors and cytokines that stimulate osteoclast activity, mainly occurring via the osteoblastic activation of receptor activator of nuclear factor κβ ligand (RANKL). RANKL activates osteoclast activity by binding to its cognitive receptor, RANK, on osteoclasts leading to increased osteolysis. The resorbing bone releases matrix-derived growth factors, such as transforming growth factor-beta (TGFβ) and insulin-like growth factor-1, resulting in continued stimulation of tumour cell proliferation, creating a vicious cycle of bone metastasis [2]. Bisphosphonates act to interrupt this vicious cycle with consequent reduction of bone-derived growth factors and cytokines, rendering bone less fertile as a site of metastatic growth.

Pharmacology of Bisphosphonates

Bisphosphonates are stable synthetic analogues of pyrophosphate, with a fundamental P-C-P backbone acting as a bone hook. Two side chains, R1 and R2, are covalently bound to the carbon atom, the structures of which vary between bisphosphonates and influence biological activity [3,4]. The presence of a nitrogen atom in the R2 side chain increases potency and essentially divides bisphosphonates into non-nitrogen-containing and nitrogen-containing bisphosphonates. After administration, bisphosphonates accumulate in bone and are selectively internalised by osteoclasts during bone resorption. Non-nitrogen-containing bisphosphonates are metabolised to hydrolysis-resistant ATP-analogues, ultimately leading to osteoclast apoptosis [3]. Nitrogen-containing bisphosphonates mainly inhibit farnesyl diphosphate synthase, a key enzyme in the mevalonate pathway, leading to an inhibition of important lipid intermediates required for the prenylation of important signaling GTPases, such as Ras, Rho and Rac [5,6], ultimately leading to osteoclast dysfunction and induction of osteoclast apoptosis.

Prevention of Cancer Treatment-induced Bone Loss

Premenopausal women are at significant risk of CTIBL associated with adjuvant treatments such as chemotherapy and endocrine therapy from suppression of oestrogen levels and premature menopause [7,8]. Chemotherapy-induced primary ovarian failure (CIOF) occurs in about 68% of patients, with a range of 20–100% depending on age (above or below 40 years), cytotoxic agent and cumulative dose [7,9], and is associated with a rapid decrease in bone mineral density (BMD) of up to 7% within 12 months [10].

Data from studies such as CALGB 79809, confirm that concomitant q3–6 monthly ZOL during the first year of chemotherapy effectively prevents CTIBL in premenopausal patients [11–13]. However, there is no long-term follow-up from these trials and therefore the clinical relevance of CTIBL in this population remains unclear with respect to longer-term fracture risk, although bone health is clearly an important concern given that many of these women have a favourable prognosis. Additionally, the optimal schedule and choice of bisphosphonate remains unclear, although it seems that oral bisphosphonates, when given in an osteoporotic dosing schedule, are not able to prevent bone loss associated with CIOF [14]. Also, not all premenopausal patients experience CIOF and therefore strategies to identify those patients who are likely to develop CIOF, or those at highest risk of CTIBL, need to be identified to be able to selectively introduce earlier treatment.

Studies have also addressed the prevention of endocrine treatment-induced bone loss in premenopausal patients. Data from the ABCSG-12 bone substudy ($n = 404$) [15], showed that the addition of ZOL to endocrine therapy alone was associated with stable BMD during the 3 years of treatment and, furthermore, an increase in BMD at 5 years (lumbar spine +4.0%, $P = 0.02$; trochanter +3.9%, $P = 0.07$) compared with baseline. In patients not receiving ZOL, there was a significant reduction in BMD at 3 years (lumbar spine −11.3%, $P < 0.001$; trochanter −7.3%, $P < 0.001$), with more dramatic effects observed in anastrozole- versus tamoxifen-treated patients. At 5 years, levels remained less than at baseline (lumbar spine −6.3%, $P = 0.001$; trochanter −4.1%, $P = 0.058$) [15]. Longer-term follow-up from this study will be important to understand if the rapid BMD loss associated with combined goserelin ± tamoxifen or anastrozole, with partial recovery by 5 years, translates into increased longer-term fracture risk and bone health concerns.

In postmenopausal women, aromatase inhibitors are the standard of care for the adjuvant endocrine treatment of hormone receptor-positive breast cancer, either as initial therapy or as sequenced treatment after 2–3 years of tamoxifen. Given that aromatase inhibition effectively depletes residual oestrogen levels by about 90% and below levels achieved in natural menopause, aromatase inhibitor treatment is associated with increased bone turnover, accelerated bone loss and an increased risk of fracture. Patients treated with 5 years of anastrozole in the ATAC bone substudy showed a median decrease in BMD of −6.1