Journal of Bone Oncology 4 (2015) 98–101

Contents lists available at ScienceDirect

Journal of Bone Oncology

journal homepage: www.elsevier.com/locate/jbo

Review Article

Dosing of zoledronic acid with its anti-tumor effects in breast cancer

Xinmin Zhao, Xichun Hu*

Department of Medical Oncology, Fudan University Shanghai Cancer Center; Department of Oncology, Shanghai Medical College, Fudan University, No. 270, Dong An Road, Shanghai 200032, China

ARTICLE INFO

Article history:
Received 25 May 2015
Received in revised form
26 August 2015
Accepted 26 August 2015
Available online 3 October 2015

Keywords:
Advanced breast cancer
Bone metastases
Zoledronic acid
N-telopeptide
Prognosis

ABSTRACT

Bisphosphonates have played an important role in the treatment of breast cancer, mainly in patients with bone metastasis, by reducing the risk of fracture, spinal cord compression, and hypercalcemia. Zoledronic acid, the most frequently used intravenous agent, has been traditionally administered on a monthly dosing schedule. Preclinical studies have demonstrated that zoledronic acid can inhibit angiogenesis, invasion, and adhesion of tumor cells. Several clinical studies of different timings and schedules of zoledronic acid therapy have demonstrated its anti-tumor effects, as well as its protective effect on bone health, in postmenopausal women during adjuvant breast cancer therapy. In general, early initiation of zoledronic acid, concomitantly with adjuvant therapy, has been found to be most beneficial. However, questions remain over the most effective schedule of treatment and relative potency of zoledronic acid. Therefore, we review the existing clinical studies to examine the influence of dosing of zoledronic acid therapy on clinical outcomes in patients with breast cancer.

1. Introduction

The bone is the most common site of tumor metastasis, in about 20–25% of cancer patients [1]. Bone metastases are most common from carcinomas of the breast, lung, prostate, kidney, and thyroid. Some bone metastases are osteoclastic, whereas others are osteoblastic or mixed, resulting from reactive bone formation.

Zoledronic acid (Zometa, Novartis) is the only bisphosphonate indicated for the management of solid tumors with bone metastases at the time of writing [2]. It is about 100–1000 times more potent than other bisphosphonates such as clodronate, pamidronate, risedronate, alendronic acid, or etidronate [3–13]. Zoledronic acid inhibits farnesyl diphosphate synthase, an enzyme in the mevalonate pathway, reducing the post-translational prenylation of proteins such as small GTPases, and resulting in the disruption of metabolic pathways essential for cancer cell survival [3,14]. Zoledronic acid may also exert indirect anti-tumor effects by modulating the immune system. It is structurally similar to low-molecular-weight, non-peptide compounds with a phosphate residue, which is recognized by gamma delta T cells in the mediation of immune responses directed against tumor cells [3].

Several dosing schedules of zoledronic acid for the treatment of osteoporosis and bone metastases have been proposed [15,16]. Several dosing schedules of zoledronic acid have been studied, including conventional dosing (4 mg intravenously every 3–4 weeks), maintenance dosing (4 mg intravenously every 3–6 months), and metronomic dosing (1 mg intravenously weekly). Different dosing schedules may have different anti-tumor effects.

2. Conventional dosing

Zoledronic acid has been demonstrated *in vitro* and *in vivo* to have anti-tumor activity. Although the approved dosing schedules of zoledronic acid (4 mg intravenously every 3–4 weeks) and pamidronate (90 mg intravenously monthly) have reduced the risk of skeletal morbidity in patients with bone metastases, the anti-tumor activity of zoledronic acid in breast cancer patients still needs to be optimized.

Levels of circulating vascular endothelial growth factor (VEGF), an critical biomarker of tumor angiogenesis, may be useful in the optimization of bisphosphonate use. Increased levels of circulating VEGF correlate with poor prognosis and negative clinical outcomes, including shortened survival, in multiple tumor types. Furthermore, preclinical studies have demonstrated that bisphosphonates are able to inhibit angiogenesis. Promising data from 2 clinical studies in patients with metastatic bone disease demonstrated that a single dose of zoledronic acid (4 mg) or pamidronate (90 mg) can reduce levels of circulating VEGF. In patients with bone metastases from late-stage solid tumors, circulating VEGF levels were analyzed after monthly treatment with zoledronic acid [16]. VEGF levels decreased 7 days after zoledronic acid infusion [16]. Similarly, in breast cancer patients with bone metastases ($N=42$), zoledronic acid significantly reduced basal VEGF

* Corresponding author. Fax: +86 21 64174774.
E-mail address: xchu2009@hotmail.com (X. Hu).

http://dx.doi.org/10.1016/j.jbo.2015.08.001

levels 3 weeks post infusion ($p < 0.0001$) [17]. Furthermore, these reductions correlated with delayed time to bone disease progression (58 versus 34 weeks; $p=0.0024$) and delayed time to first skeleton related events (SRE) (76 versus 39 weeks; $p=0.0002$) compared with patients whose VEGF levels remained elevated. Zoledronic acid has been clinically evaluated for potential anti-angiogenic effects in patients with bone metastases from advanced cancers [15]. In patients who received zoledronic acid, circulating levels of VEGF decreased after 1 week ($p=0.04$) [15]. This inhibition persisted throughout the 84-day observation period of the study ($p \leq 0.014$). Since changes in levels of serum VEGF correlated with clinical outcomes, zoledronic acid-mediated suppression of serum VEGF levels may decrease tumor burden in patients with advanced and metastatic cancers. The anti-tumor activity of conventional zoledronic acid was also assessed in a study of patients with multiple myeloma ($N=94$) who were randomized to receive standard anti-cancer therapy with or without a conventional (4 mg monthly) dose of zoledronic acid [18]. Patients who received zoledronic acid had significantly improved progression free survival (PFS) (20% versus 48%; $p < 0.01$), event-free survival (80% versus 52%; $p < 0.01$), and overall survival (OS) (80% versus 46%; $p < 0.01$) compared with patients who received only anticancer therapy, as well as a reduction in the incidence of skeletal-related events [18]. Since all patients received the same anti-cancer treatment in the same setting, the improved clinical results of zoledronic acid-containing regimen were attributed to the anti-tumor activity of zoledronic acid. Preliminary clinical data regarding the anti-tumor activity of conventional setting of zoledronic acid are encouraging, but further analyses are required to confirm the optimal treatment setting.

3. Bone half-life based dosing

As zoledronic acid has been shown to have anti-tumor efficacy in both the pre-clinical and clinical settings using the conventional regimen (zoledronic acid 4 mg infusion 4 weekly), some studies were designed to explore the anti-tumor effects of zoledronic acid when administered continuously every 6 months. In ABSCG-12, 1803 premenopausal women that compares the efficacy and safety of anastrozole or tamoxifen with or without zoledronic acid (4 mg every 6 months) for 3 years. At a median follow-up of 62 months, Zoledronic acid (4 mg every 6 months) with adjuvant endocrine therapy significantly improved DFS versus endocrine therapy without zoledronic acid (92% versus 88%, respectively; log-rank $p=0.008$). This 4% absolute difference in DFS corresponded to a significant reduction in the relative risk of events for patients receiving versus not receiving zoledronic acid, stratified by endocrine therapy (76 versus 110 events; HR 0.68, 95% confidence interval [CI] 0.51–0.91, Cox $p=0.009$, log-rank $p=0.008$). Zoledronic acid significantly reduced the relative risk of DFS events both in node-positive (HR 0.67, 95% CI 0.45–0.99) and node-negative patients (HR 0.66, 95% CI 0.43–1.03). Fewer patients receiving zoledronic acid had distant disease recurrence at both bone and non-bone sites (44 versus 56 events), including contralateral breast cancer (6 versus 8 events) and locoregional recurrence (15 versus 30 events). In a subgroup analysis by patient age at study entry, a treatment by-covariate interaction based on patients aged 40 years or younger versus those older than 40 years did not reveal significant heterogeneity ($p=0.121$). However, in patients who were 40 years or younger at baseline ($N=413$), zoledronic acid did not significantly reduce the relative risk of DFS events (HR 0.94, 95% CI 0.57–1.56), whereas in those who were older than 40 years at study entry ($N=1390$), the risk reduction with in patients treated with zoledronic acid was significant (HR 0.58, 95% CI 0.40–0.83). Thirty deaths (3% of 900 patients) occurred in the zoledronic acid group, whereas 43 deaths (5% of 903 patients) occurred in the non-zoledronic acid group; risk of death did not differ significantly between these groups (HR 0.67, 95% CI 0.41–1.07; Cox $p=0.09$). OS also did not differ significantly between treatment groups in patients with node-positive (HR 0.62, 95% CI 0.34–1.15) and node-negative disease (HR 0.70, 95% CI 0.33–1.52). The addition of zoledronic acid improved DFS in patients taking either anastrozole or tamoxifen. These data show consistent benefits with zoledronic acid and support its addition to adjuvant endocrine therapy in premenopausal patients with early-stage breast cancer [19].

In the ZO-FAST study, 1065 women were randomly assigned to immediate zoledronic acid 4 mg every 6 months for 5 years, or delayed zoledronic acid. Patients were administered letrozole for a median of approximately 60 months. After 5 years of follow-up, patients in the immediate-zoledronic acid group had a 34% relative reduction in the risk of DFS events versus the delayed-zoledronic acid group, HR 0.66, 95% CI 0.44–0.97, $p=0.0375$). Fewer local and distant disease recurrences occurred in the immediate-zoledronic acid group versus the delayed-zoledronic acid group (local recurrences, 0.9% versus 2.3%, respectively; distant recurrences, 5.5% versus 7.7%, respectively). Bone metastases were more common in the delayed-zoledronic acid group versus the immediate-zoledronic acid group (4.5% versus 2.6%, respectively). Contralateral breast cancers were reported in 3 patients in the immediate-zoledronic acid group versus 6 in the delayed-zoledronic acid group. Immediate use of zoledronic acid substantially improved DFS versus patients in the delayed arm (HR 0.62, 95% CI 0.41–0.93; $p=0.0239$). Exploratory analyses showed that zoledronic acid initiation in this group ($N=144$) improved DFS versus no zoledronic acid treatment (HR 0.46, $p=0.0334$). A larger (non-significant) proportion of patients initiating delayed zoledronic acid treatment were lymph node-positive at diagnosis (70%) compare to those not initiating delayed zoledronic acid (55%), which may contribute to an underestimate of the DFS benefits from delayed introduction of zoledronic acid. Other prognostic factors identified for DFS in the delayed-zoledronic acid arm included tumor stage (HR 2.16, $p=0.0416$ for $\geq$T2 versus T0 or T1) and age (HR 1.95, $p=0.0236$ for age ≥ 65 versus < 65 years). Further exploratory analyses showed trends towards improved DFS with immediate zoledronic acid in recently menopausal ($N=177$) and truly postmenopausal ($N=888$) patients ($0.05 < p < 0.1$). In exploratory analyses of women with established postmenopausal status (> 5 years postmenopausal or > 60 years of age at study entry; $N=670$), immediate zoledronic acid was associated with a trend for improved DFS (HR 0.63, $p=0.0516$) and demonstrated substantially improved OS (HR 0.50, $p=0.0224$) versus delayed zoledronic acid. These findings show that, in addition to improving bone health, initiating zoledronic acid immediately may improve DFS compared with delaying zoledronic acid [20].

In the phase 3 AZURE trial, 3360 women were randomly assigned to receive standard adjuvant systemic treatment alone (control group) or with 4 mg intravenous zoledronic acid every 3–4 weeks for 6 doses, then every 3 months for 8 doses, followed by every 6 months for 5 doses, for a total of 5 years of treatment. The number of DFS events did not differ between the 2 groups. DFS, OS, and distant recurrences were also similar in both groups. However, zoledronic acid reduced the development of bone metastases, both as a first event (HR 0.78, 95% CI 0.63–0.96; $p=0.020$) and at any time during follow-up (HR 0.81, 95% CI 0.68–0.97; $p=0.022$). The effects of zoledronic acid on DFS were not affected by estrogen receptor (ER) status. However, zoledronic acid improved IDFS in those who were over 5 years since menopause at trial entry ($N=1041$; HR 0.77, 95% CI 0.63–0.96) but not in all other (premenopause, perimenopause, and unknown status) menopausal groups ($N=2318$; HR 1.03, 95% CI 0.89–1.20). For postmenopausal women with stage II or III breast cancer, the absolute