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

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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

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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

DFS benefit at 5 years of around 5% and an osteonecrosis of the jaw rate of 1–2% suggest a favorable risk-to-benefit ratio. Overall, these data do not support the use of adjuvant zoledronic acid in unselected patients with early breast cancer. However, these data suggest that zoledronic acid can be used for postmenopausal women with early breast cancer who are receiving adjuvant treatment [21,22].

Recently, a meta-analysis on 18,766 women with median follow-up 5.6 years showed that by using bisphosphonates including zoledronic acid, the reductions in recurrence (RR 0.·94, 95% CI 0.87–1.01; 2p=0.08), distant recurrence (0.92, 0.85–0.99; 2p=0.03), and breast cancer mortality (0.91, 0.83–0.99; 2p=0.04) were of only borderline significance, but the reduction in bone recurrence was more significant (0.83, 0.73–0·94; 2p=0.004). Even for bone recurrence, however, the heterogeneity of benefit was barely significant by age (2p=0.03) and menopausal status (2p=0.06 for trend with menopausal status), and it was non-significant by bisphosphonate class, treatment schedule, estrogen receptor status, nodes, etc. No differences were seen in non-breast cancer mortality. Bone fractures were reduced (RR 0.85, 95% CI 0.75–0.97; 2p=0.02). Hence, adjuvant bisphosphonates including zoledronic acid was able to reduce the rate of breast cancer recurrence in the bone and improve breast cancer survival, but there is significant benefit only in postmenopausal women [23].

4. Blood half-life based use

On the basis of promising data from an *in vivo* study suggesting that low-dose weekly regimens of zoledronic acid were able to reduce skeletal tumor burden, Santini et al. designed a study to explore the potential anti-angiogenic effect of a weekly low-dose therapy with zoledronic acid in patients with malignancies. Twenty-six patients with solid cancer and bone metastases were administered 1 mg of zoledronic acid weekly for 4 times followed by 4 mg of zoledronic acid over a standard 4-week schedule, repeated 3 times. The median VEGF basal level showed a statistically significant ($p=0.038$) decrease 7 days after the first 1 mg dose of zoledronic acid, and this effect persisted after 1 mg infusions at 14 ($p=0.002$), 21 ($p=0.001$), and 28 days ($p=0.008$). Moreover, the decrease in circulating VEGF levels persisted at each prespecified time point during the second phase of the study (zoledronic acid 4 mg every 4 weeks) [24].

Based on these preliminary clinical results with low-dose, intermittent zoledronic acid, Hu et al. conducted a randomized phase II clinical study in order to clarify the role of metronomic low-dose zoledronic acid. Sixty breast cancer patients with bone metastases were randomized to receive either 1 mg intravenous zoledronic acid weekly for 4 doses, or a single 4 mg intravenous dose of zoledronic acid. Administration of other treatments was delayed for 1 month. Serial blood samples were collected on days 1, 15, 29, and at 3 months. Serum VEGF alteration was the primary endpoint. Compared to the conventional arm, the metronomic arm exhibited a significantly greater reduction in serum levels of VEGF and N-telopeptide of type I collagen (NTx) during the first month of treatment. Serum CA 15-3 level stabilized over time in the metronomic arm, but increased in the conventional arm. Independent prognostic factors for PFS included chemotherapy received (HR 8.042, $p=0.000$), ER status (HR 2.837, $p=0.020$), VEGF levels at 3 months after intervention (HR 2.026, $p=0.045$), and baseline NTx (HR 1.051, $p=0.001$). This is the first study to demonstrate that metronomic weekly low-dose zoledronic acid could be more effective than the conventional zoledronic acid dosing schedule. The weekly regimen resulted in more effective suppression of circulating VEGF and NTx levels, and possibly, more effective stabilization of serum tumor markers. Intervention-related VEGF levels at 3 months after zoledronic acid treatment are an independent prognostic factor for PFS. Further evaluation of the clinical and biomarker parameters of the metronomic (q 1 week) zoledronic acid regimen is clearly warranted [24]. Therefore, the prognostic and predictive effects of clinical and biochemical factors were examined in the aforementioned randomized study of a weekly low dose (metronomic arm) versus a conventional dosage of zoledronic acid (conventional arm) in breast cancer patients with bone metastases. Specifically, treatment outcomes in 60 patients with bone metastases were used to assess the impacts of the following potential prognostic factors: ER status, lymph node status, 2-year disease-free interval (DFI), numbers of chemotherapy regimens administered, interventions, serum levels of VEGF, NTx, CEA, and CA 15-3. In univariate analyses, patients pretreated with 2 or fewer chemotherapy regimens, patients with ER-positive tumors, patients with 3 or fewer lymph nodes, patients with DFI of more than 2 years, patients with serum VEGF of less than 500 pg/mL after 3 months of intervention, patients with serum CEA and CA 15-3 of less than ULN, and patients with baseline serum NTx of less than 18 nM BCE had significantly longer PFS. Multivariate analysis showed that ER positivity (HR 0.295; 95% CI 0.141–0.618, $p=0.001$), serum VEGF of less than 500 pg/mL after 3 months of intervention (HR 2.220, 95% CI 1.136–4.338, $p=0.020$), baseline serum NTx of less than 18 nM BCE (HR 2.842, 95% CI 1.458–5.539, $p=0.001$), and 2 or fewer chemotherapy regimens received (HR 7.803, 95% CI 2.884–21.112, $p=0.000$) were associated with better PFS. When evaluating the predictive effect of the biochemical factors, an interaction between NTx and zoledronic acid intervention was shown ($p=0.005$). The HR of weekly low dose versus conventional zoledronic acid dosage was estimated to be 2.309 (99% CI 1.067–5.012) in patients with baseline serum NTx of more than 18 nM BCE. In conclusion, these results indicate superiority of weekly low dose of zoledronic acid over conventional dosing. ER, serum VEGF level after intervention, and numbers of chemotherapy regimens administered are prognostic but not predictive factors in breast cancer patients with bone metastases. Patients with baseline serum NTx of more than 18 nM BCE might benefit more from weekly low-dose of zoledronic acid [26]. Clinical results with low-dose, intermittent zoledronic acid are consistent with those observed in animal models, providing a rationale for further investigations of alternative dosing regimens to optimize the anti-tumor potential of zoledronic acid.

5. Biomarker-driven dosing

Bone turnover biomarkers offer an avenue to evaluate the ongoing rate of skeletal metabolism and interactions between cancer and skeleton in patients. The mutual effect between cancer and bone decouples activities spatially and disturbs otherwise balanced activities resulting in elevated rates of osteolysis and osteogenesis. During this process high levels of distinct biochemical markers are released into blood or urine that are amenable to non-invasive detection [24]. Bone metabolism biochemical markers can provide meaningful evidence that tumor growth influences ongoing bone turnover rate. Such biochemical markers include cross-linked collagen peptides broken from osteolysis, (e.g. the amino [N]- and carboxy [C]-terminal cross-linked telopeptides of type I collagen [NTX and CTX]) and the terminal peptides cleaved from procollagen before its incorporation into newly synthesized bone matrix (e.g. procollagen type I N-terminal and C-terminal peptides [PINP and PICP]). Serum CTX and the urinary NTX are correlated with the ongoing osteolysis rates, whereas serum bone-specific alkaline phosphatase (bone ALP) and PINP are correlated with the ongoing osteogenesis rates [24]. Bone metabolism marker such as

osteocalcin is associated with both the processes of osteolysis and osteogenesis. In general, bone metabolism biochemical markers connect with the ongoing rates of osteolysis and osteogenesis. Bone marker level variation is not disease specific, and is independent of the underlying cause of skeletal metabolism alteration [25]. Metabolism biochemical markers, on the whole, may not predict specific lesion site. Emerging evidence suggests that bone markers are helpful in identifying patients with high risk of bone metastasis and bone lesion progression [24,25]. Potential application of bone metabolism biochemical markers should be evaluated in clinical trials to identify the true value in clinical practice [27,28].

6. Future research and challenges

The utility of zoledronic acid as adjuvant or neoadjuvant therapy for its anti-tumor effects in breast cancer is currently being investigated in several clinical trials, including SWOG S0307, SUCCESS, and Natan. SWOG S0307 is a trial of bisphosphonates as adjuvant therapy for primary breast cancer. The main purpose of this phase III trial is to study the efficacy of zoledronic acid compared with clodronate or ibandronate in treating women who have undergone surgery for stage I, stage II, or stage III breast cancer. The primary endpoints are DFS and OS, assessed every 6 months for the first 5 years and then annually for 5 years, or until death or recurrence. The study was designed to enroll 5400 patients.

SUCCESS A and C are randomized, open-label, 2×2 factorial design phase III studies in patients with high-risk of breast cancer (stage N1, or T2–T4, or grade 3, or age ≤ 35 years, or hormone-receptor negative). The aim of this study is to evaluate the predictive value of zoledronic acid treatment on the prevalence of CTCs at 5 years after primary diagnosis, in addition to other well-known predictors. Patients were first randomized to adjuvant chemotherapy treatment with 3 cycles of FEC, followed by either 3 cycles of docetaxel (SUCCESS A), or 3 cycles of gemcitabine-docetaxel (SUCCESS C). In addition, patients were randomized to 2 years versus 5 years of zoledronic acid treatment. Very recently, it has been shown that zoledronic acid treatment duration has no effect on the prevalence of CTCs 5 years after primary diagnosis from 2014 SABCS. However, the same results also confirmed that CTCs may persist after standard adjuvant therapy. Immediately after Ctx, CTCs seem to be more prevalent in patients with HER2-positive tumors compared with other molecular subtypes. Other trials in this setting may provide additional information on the predictive role of CTCs in the context of bisphosphonate treatment.

The Natan study is comparing neoadjuvant therapy with or without zoledronic acid, and is a study that we are following closely. It is a randomized, multicenter, open-label phase III study comparing the postoperative use of zoledronic acid with no postoperative treatment in patients with histological tumor residuals after preoperative anthracycline and taxane-containing chemotherapy for primary breast cancer. The primary endpoint is 5-year event-free survival from the time of postoperative treatment.

Data from these studies will provide important insights into the anti-tumor effects of zoledronic acid, especially in postmenopausal breast cancer patients. We believe that more studies should be designed in this population to further explore suitable dosing and duration of zoledronic acid therapy, and to further understand its mechanisms of action.

7. Conclusions

In addition to its effects on BMD and bone remodeling, zoledronic acid has potent anti-tumor effects. These are related to its dosing schedule and to patient factors, such as the low estrogen environment in post-menopausal breast cancer patients. Four-weekly or 6-monthly administration of this agent can improve the prognosis of cancer patients, while a 1 mg weekly low-dose may have stronger anti-tumor effects. However, these hypotheses need to be evaluated by further clinical studies.

References

[1] H.L. ABRAMS, R. SPIRO, N. GOLDSTEIN, Metastases in carcinoma; analysis of 1000 autopsied cases, Cancer 3 (1) (1950) 74–85.
[2] A. Osborne, Zoledronic acid, Clin. J. Oncol. Nurs. 6 (6) (2002) 365–366.
[3] T.A. Guise, Antitumor effects of bisphosphonates: promising preclinical evidence, Cancer Treat. Rev. 34 (Suppl 1) (2008) S19–S24.
[4] A. Lipton, Emerging role of bisphosphonates in the clinic–antitumor activity and prevention of metastasis to bone, Cancer Treat. Rev. 34 (Suppl 1) (2008) S25–S30.
[5] P.D. Ottewell, et al., Antitumor effects of doxorubicin followed by zoledronic acid in a mouse model of breast cancer, J. Natl. Cancer Inst. 100 (16) (2008) 1167–1178.
[6] E.F. Solomayer, et al., Influence of zoledronic acid on disseminated tumor cells in primary breast cancer patients, Ann. Oncol. 23 (9) (2012) 2271–2277.
[7] E. Giraudo, M. Inoue, D. Hanahan, An amino-bisphosphonate targets MMP-9-expressing macrophages and angiogenesis to impair cervical carcinogenesis, J. Clin. Invest. 114 (5) (2004) 623–633.
[8] M.F. Gnant, et al., Zoledronic acid prevents cancer treatment-induced bone loss in premenopausal women receiving adjuvant endocrine therapy for hormone-responsive breast cancer: a report from the Austrian Breast and Colorectal Cancer Study Group, J. Clin. Oncol. 25 (7) (2007) 820–828.
[9] M. Gnant, et al., Endocrine therapy plus zoledronic acid in premenopausal breast cancer, N. Engl. J. Med. 360 (7) (2009) 679–691.
[10] A. Brufsky, et al., Integrated analysis of zoledronic acid for prevention of aromatase inhibitor-associated bone loss in postmenopausal women with early breast cancer receiving adjuvant letrozole, Oncologist 13 (5) (2008) 503–514.
[11] R.E. Coleman, Adjuvant bisphosphonates in breast cancer: are we witnessing the emergence of a new therapeutic strategy? Eur. J. Cancer 45 (11) (2009) 1909–1915.
[12] R.T. Chlebowski, et al., Oral bisphosphonate use and breast cancer incidence in postmenopausal women, J. Clin. Oncol. 28 (22) (2010) 3582–3590.
[13] G. Rennert, M. Pinchev, H.S. Rennert, Use of bisphosphonates and risk of postmenopausal breast cancer, J. Clin. Oncol. 28 (22) (2010) 3577–3581.
[14] J.E. Kim, et al., Zoledronic acid prevents bone loss in premenopausal women with early breast cancer undergoing adjuvant chemotherapy: a phase III trial of the Korean Cancer Study Group (KCSG-BR06-01), Breast Cancer Res. Treat. 125 (1) (2011) 99–106.
[15] D. Santini, et al., Repeated intermittent low-dose therapy with zoledronic acid induces an early, sustained, and long-lasting decrease of peripheral vascular endothelial growth factor levels in cancer patients, Clin. Cancer Res. 13 (2007) 4482–4486 15 Pt 1.
[16] D. Santini, et al., Pamidronate induces modifications of circulating angiogenetic factors in cancer patients, Clin. Cancer Res. 8 (5) (2002) 1080–1084.
[17] B. Vincenzi, et al., Zoledronic acid-related angiogenesis modifications and survival in advanced breast cancer patients, J. Interferon Cytokine Res. 25 (3) (2005) 144–151.
[18] A. Aviles, et al., Antitumor effect of zoledronic acid in previously untreated patients with multiple myeloma, Med. Oncol. 24 (2) (2007) 227–230.
[19] M. Gnant, et al., Adjuvant endocrine therapy plus zoledronic acid in premenopausal women with early-stage breast cancer: 62-month follow-up from the ABCSG-12 randomised trial, Lancet Oncol. 12 (7) (2011) 631–641.
[20] R. Coleman, et al., Zoledronic acid (zoledronate) for postmenopausal women with early breast cancer receiving adjuvant letrozole (ZO-FAST study): final 60-month results, Ann. Oncol. 24 (2) (2013) 398–405.
[21] R. Coleman, et al., Adjuvant zoledronic acid in patients with early breast cancer: final efficacy analysis of the AZURE (BIG 01/04) randomised open-label phase 3 trial, Lancet Oncol. 15 (9) (2014) 997–1006.
[22] K. Harnden, K. Blackwell, Routine use of zoledronic acid in early-stage breast cancer, J. Natl. Compr. Cancer Netw. 13 (4) (2015) 480–486.
[23] Adjuvant bisphosphonate treatment in early breast cancer, meta-analyses of individual patient data from randomised trials, Lancet (2015).
[24] D. Santini, et al., Repeated intermittent low-dose therapy with zoledronic acid induces an early, sustained, and long-lasting decrease of peripheral vascular endothelial growth factor levels in cancer patients, Clin. Cancer Res. 13 (15) (2007) 4482–4486.
[25] X. Zhao, et al., Biomarker alterations with metronomic use of low-dose zoledronic acid for breast cancer patients with bone metastases and potential clinical significance, Breast Cancer Res. Treat. 124 (3) (2010) 733–743.
[26] X. Zhao, et al., Prognostic and predictive value of clinical and biochemical factors in breast cancer patients with bone metastases receiving "metronomic" zoledronic acid, BMC Cancer 11 (2011) 403.
[27] J.R. Gralow, et al., NCCN task force report: bone health in cancer care, J. Natl. Compr. Cancer Netw. 11 (Suppl 3) (2013), S1-50; quiz S51.
[28] R. Coleman, et al., Bone health in cancer patients: ESMO clinical practice guidelines, Ann. Oncol. 25 (suppl 3) (2014) iii124–iii137.