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An Evolving Role of Antitumor Activity of Zoledronic Acid in Breast Cancer

S Nanditha[1*], Polusani Pratham[2], Mullapudi Surendranadh Chowdary[3*] and Vineela Kanneboyina[4]

[1]Rajarajeswari Medical College and Hospital, Bengaluru, Karnataka, India
[2]Government Medical College, Nizamabad, Telangana, India
[3]GSL Medical College & General Hospital, Rajahmundry, Andhra Pradesh, India
[4]Narayana Medical College and Hospital, Nellore, Andhra Pradesh, India

Abstract

Breast cancer patients with bone metastases benefit from bisphosphonates by reducing fracture risks, spinal cord compression, and hypercalcemia caused by bone metastases. Traditionally, zoledronic acid has been administered on a monthly schedule via intravenous injection. It has been demonstrated in preclinical studies that zoledronic acid can inhibit tumor cell invasion, adhesion, and angiogenesis. The anti-tumor effects and bone health benefits of zoledronic acid therapy have been demonstrated in several clinical studies conducted with postmenopausal women during adjuvant breast cancer treatment at various timings and schedules. According to several observations and postmenopausal data, zoledronic acid's anticancer activity may be affected by the endocrine environment. It appears zoledronic acid may be most effective for improving disease-free survival in women who are postmenopausal or have endocrine therapy-induced menopause in the adjuvant setting. In general, zoledronic acid is most effective when initiated early, concomitantly with adjuvant therapy. Still, zoledronic acid's relative potency and the most effective schedule of treatment remain unclear. To examine the effectiveness of zoledronic acid therapy in patients with breast cancer, we reviewed existing clinical studies.

Keywords: Zoledronic acid, Advanced breast Cancer, Bone metastases

[*]***Correspondence to:*** S Nanditha and Mullapudi Surendranadh Chowdary, Rajarajeswari Medical College and Hospital, Bengaluru, Karnataka, India and GSL Medical College & General Hospital, Rajahmundry, Andhra Pradesh, India.

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Introduction

A cancer patient's bone is the most common site of tumor metastasis, accounting for about 20 - 25% of all cancers. In addition to cancers of the breast, the lung, the prostate, the kidney, and the thyroid, bone metastases are also common. Reactive bone formation results in some osteoclastic metastases, while others are osteoblastic or mixed [1]. Approximately 2.1 million new cases of breast cancer are diagnosed each year, making it the leading cause of cancer deaths among women. In the United States, one in eight women is at risk of developing breast cancer during their lifetime [2]. It is still challenging to prevent local or distant relapse after surgery and adjuvant treatment, even in patients with no evidence of residual disease. Patients with metastatic breast cancer often experience bone recurrence, with up to 80% developing lesions in the bone. Hematopoietic niches are supported by the bone marrow, which is highly vascularized and contains a number of growth factors, cytokines, and other signaling molecules. In addition to protecting pluripotent hematopoietic stem cells from immune activity and other attacks, this environment can act as an inadvertent sanctuary for cancer cells [3-6]. Consequently, bone microenvironment may act as a shield against chemotherapeutic agents, thereby promoting cancer cell survival and tumor growth.

As of the time of writing, the only bisphosphonate indicated for solid tumors with bone metastases is zoledronic acid. As compared to clodronate, pamidronate, risedronate, alendronic acid, and etidronate, it is about 100 - 1000 times more potent. Inhibiting farnesyl diphosphate synthase, a mevalonate pathway enzyme, causes zoledronic acid to reduce post-translational prenylation of proteins, disrupting essential metabolic pathways of cancer cells [7]. In addition to its direct antitumor effects, zoledronic acid may modulate the immune system indirectly as well. This compound contains a phosphate residue, which is recognized by gamma delta T cells in the mediation of immune responses against tumor cells. For the treatment of osteoporosis and bone metastases, zoledronic acid has been administered according to several dosing schedules. Zoledronic acid has been studied in a variety of dose schedules, including conventional doses (4 mg intravenously every 3 to 4 weeks), maintenance doses (4 mg intravenously every 3 to 6 months), and metronomic doses (1 mg intravenously weekly). Dosing schedules may have different anti-tumor effects [8].

Zoledronic acid

A bisphosphonate is an antiresorption agent that inhibits bone resorption caused by osteoclasts. By attaching to the mineralized bone matrix and ingesting osteoclasts during osteolysis, bisphosphonates inhibit osteoclast-mediated bone resorption. Due to its nitrogen content, zoledronic acid also inhibits the activity of farnesyl diphosphate synthase, an enzyme involved in the mevalonate pathway, reducing the activity, proliferation, and viability of cells ingesting this agent (e.g.,osteoclasts actively resorbing bone and cancer cells) [9].

There is a possibility that zoledronic acid's anticancer activity is mediated by its effects on the bone marrow microenvironment. Zoledronic acid inhibits bone metastases by rendering the

bone microenvironment less conducive to cancer cell survival and proliferation. Besides zoledronic acid's effects on the bone microenvironment, preclinical evidence suggests that it may also interfere with other cancer progression and tumor growth processes. A number of indirect mechanisms are involved in zoledronic acid's anticancer activity, including the activation of anticancer immune responses, inhibition of angiogenesis, and inhibition of interactions with mesenchymal stem cells. Bone metastases are not the only ramifications of these activities. Cancer cell invasion and migration can be profoundly inhibited by inhibiting the interaction between mesenchymal stem cells and cancer cells. As a result, skeletal and extraskeletal metastases might be limited (Figure 1) [10-13].

As a direct anticancer agent, zoledronic acid inhibits cancer cell growth and survival, as well as synergizing with anticancer therapies. Translational studies have also demonstrated that zoledronic acid stimulates an immune response against cancer. As a side effect, it is also capable of reducing the persistence and number of disseminated tumor cells in bone marrow [14]. Angiogenic growth factors are also reduced by it. In view of the complexity of the process of metastatic spread from solid tumors, it is likely that zoledronic acid has anticancer properties both inside and outside of the bone due to a variety of anticancer mechanisms of action demonstrated in preclinical and translational studies.

Dosing

It has been demonstrated *in vitro* and *in vivo* that zoledronic acid has 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, it is still necessary to optimize zoledronic acid's antitumor activity in breast cancer patients. A critical biomarker of tumor angiogenesis, circulating vascular endothelial growth factor (VEGF), may assist in optimizing bisphosphonate therapy [15]. Multiple tumor types are associated with increased levels of circulating VEGF and poor outcomes, including shorter survival times. Angiogenesis has also been shown to be inhibited by bisphosphonates in preclinical studies. A single dose of zoledronic acid (4 mg) or pamidronate (90 mg) reduced

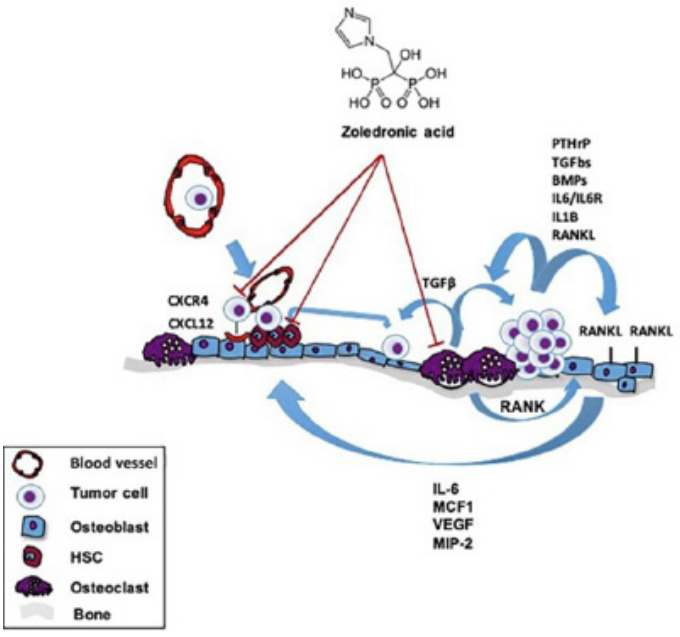

Figure 1: Effects of zoledronic acid [13].

levels of circulating VEGF in metastatic bone disease patients in two clinical studies. Zoledronic acid treatment was administered monthly to patients with late-stage solid tumor bone metastases [16]. A 7-day zoledronic acid infusion decreased VEGF levels. Similar results were found in patients with breast cancer and bone metastases (N = 42) after zoledronic acid infusions ($p < 0.0001$). These reductions also correlated with a delayed time to bone disease progression (58 vs 34 weeks; $p = 0.0024$) and a delayed time to first skeleton-related events (76 vs 39 weeks; $p = 0.0002$) when compared with patients with elevated VEGF levels [17]. Clinical trials have been conducted on zoledronic acid to determine if it has antiangiogenic effects in patients with advanced cancers who have developed bone metastases. A decrease in circulating VEGF levels was observed in patients receiving zoledronic acid after 1 week ($p = 0.04$). Over the course of the study's 84-day observation period, this inhibition continued to persist ($p \leq 0.014$). In patients with advanced and metastatic cancers, zoledronic acid-mediated suppression of serum VEGF levels may decrease tumor burden due to its correlation with clinical outcomes. Patients with multiple myeloma (N = 94) randomized to receive standard anti-cancer therapy with or without a conventional (4 mg monthly) dose of zoledronic acid had a positive response to conventional zoledronic acid. As compared with patients who received only anticancer therapy, those who received zoledronic acid had significantly longer progression-free survival (20% vs 48%; $p < 0.01$), event-free survival (80% vs 52%; $p < 0.01$), and overall survival (OS) (80% vs 46%; $p < 0.01$), along with a significant reduction in skeletal-related events. The improved clinical results of zoledronic acid-containing regimens were attributed to the antitumor activity of the drug because all patients received the same anticancer treatment in the same setting. Despite preliminary clinical data showing anti-tumor activity of zoledronic acid in conventional settings, further analyses are needed to determine the optimal treatment setting [18].

Blood half-life-based usage and Bone half-life-based dosing

According to Santini et al. [12] low-dose weekly zoledronic acid regimens reduced skeletal tumor burden based on promising data from an *in vivo* study. The purpose of the study was to determine if weekly low-dose zoledronic acid therapy might be anti-angiogenic for patients with malignancies. Twenty-six patients with solid cancer and bone metastases were treated with 1 mg zoledronic acid each week for four weeks, followed by 4 mg zoledronic acid every other week for three weeks [19]. After the first dose of 1 mg zoledronic acid, the median VEGF basal level decreased statistically significantly, and after infusions of 1 mg at 14 , 21, and 28 days, the effect persisted. Moreover, the decrease in circulating VEGF levels persisted during each prespecified time point during the second phase. To clarify the role of metronomic low-dose zoledronic acid, Coleman et al. [20] conducted a randomized phase II clinical trial based on preliminary clinical results with low-dose, intermittent zoledronic acid. Sixty female breast cancer patients with bone metastases were randomized to either receive 1 mg intravenous zoledronic acid weekly for four doses, or a single dose of 4 mg intravenous zoledronic acid. It took one month for other treatments to be administered. Blood samples were collected every day for the first 15 days, 29 days, and 3 months thereafter [20-23]. A primary endpoint was the alteration of serum VEGF. Metronomic treatment significantly reduced serum levels of VEGF and N-telopeptide of type I collagen (NTx) during the first month of treatment compared to conventional treatment. Compared to the conventional arm, the serum CA 15-3 level stabilized over time in the metronomic arm. Chemotherapy received was associated with the longest PFS, ER status was associated with the longest PFS, VEGF levels were associated with the longest PFS, and baseline NTx was associated with the longest PFS. It is the first study to demonstrate that low-dose metronomic zoledronic acid

could be more effective than conventional zoledronic acid dosing [2, 24]. As a result of the weekly regimen, serum tumor markers were more effectively stabilized, and circulating VEGF and NTx levels were effectively reduced. After zoledronic acid treatment, intervention-related VEGF levels are an independent prognostic factor. It is evident that metronomic zoledronic acid regimens require further evaluation of clinical and biomarker parameters [25]. It was therefore examined in the aforementioned randomized study of breast cancer patients with bone metastases whether clinical and biochemical factors affected prognosis and prediction. A weekly low dose of zoledronic acid (metronomic arm) was compared with a conventional dosage (conventional arm). In specific, the impact of the following potential prognostic factors on the treatment outcomes of 60 patients with bone metastases was assessed: ER status, lymph node status, 2-year disease-free interval (DFI), number of chemotherapy regimens, interventions, serum levels of VEGF, NTx, CEA, and CA 15-3. The PFS of patients pretreated with two or fewer chemotherapy regimens, those with ER-positive tumors, those with three or fewer lymph nodes, patients with DFI of over 2 years, patients whose serum VEGF after 3 months was lower than 500 pg/ml, patients whose serum CEA and CA 15-3 were lower than their ULN, and those whose baseline serum NTx was less than 18 nM BCE were significantly longer [26]. After multivariate analysis, serum VEGF was lower than 500 pg/ml after 3 months of intervention, serum NTx was lower than 18 nm, and two or fewer chemotherapy regimens were associated with better PFS. The biochemical factors NTx and zoledronic acid interacted when evaluating the predictive effect. Based on the baseline serum NTx of more than 18 nm BCE, a weekly low dose zoledronic acid dosage was estimated to have a HR of 2.309. These results indicate that a weekly low dose of zoledronic acid is superior to a conventional dose. A patient's ER level, serum VEGF levels after intervention, and the number of chemotherapy regimens they received are prognostic, but not predictive. Low dose zoledronic acid might benefit patients with baseline serum NTx over 18 nM BCE. The results obtained with intermittent, low-dose zoledronic acid are consistent with those observed in animal models, which supports further studies of alternative dosing regimens to maximize zoledronic acid's antitumor properties [27-29].

Whereas bone half-life-based dosing, the conventional regimen of zoledronic acid (zoledronic acid infusion 4 mg 4 weekly) has been shown to be effective in both preclinical and clinical settings for treating tumors. Some studies investigated whether zoledronic acid had anti-tumor effects when continuously administered every six months. For a three-year period, 1803 premenopausal women were randomized to receive anastrozole or tamoxifen with or without zoledronic acid (4 mg every 6 months) [30]. DFS was significantly improved with Zoledronic acid (4 mg every 6 months) plus adjuvant endocrine therapy (92% versus 88%, respectively; log-rank p = 0.008) at a median follow-up of 62 months. As a result of this 4% difference in the absolute DFS, the relative risk of events decreased significantly for patients taking zoledronic acid versus not taking it (84 vs 130 events; HR 0.68, 95% confidence interval [CI]). Node-positive and node-negative patients were both significantly reduced by zoledronic acid. Patients receiving zoledronic acid experienced fewer distant disease recurrences at both bone and non-bone sites (39 vs 55 events), including contralateral breast cancer (7 vs 9 events) and locoregional recurrence (18 vs 42 events). In a subgroup analysis based on patient age at study entry, a treatment by covariate interaction was not significantly different between patients under 40 years old and those over 40 years old [31]. A significant reduction in the risk of DFS events was found, however, in patients who were 40 or younger at baseline, whereas in patients who were older than 44 years at study entry, zoledronic acid significantly reduced the risk. Zoledronic acid was associated with thirty deaths, while non-zoledronic acid was associated with 43 deaths; risk of death did not differ significantly between these two groups. When zoledronic acid was added to anastrozole or tamoxifen, DFS improved. Based on these data, zoledronic acid may be beneficial to premenopausal breast cancer patients who are undergoing adjuvant endocrine therapy.

1065 women participated in the ZO-FAST trial, which randomly assigned them to receive immediate or delayed zoledronic acid 4 mg every 6 months for five years. Approximately 60 months of letrozole were administered to patients. In the immediate-zoledronic acid group, DFS events were 34% lower than those in the delayed-zoledronic acid group after 5 years. Compared to the delayed-zoledronic acid group, the immediate-zoledronic acid group experienced fewer local and distant recurrences. Compared with the immediate-zoledronic acid group, the delayed-zoledronic acid group had more bone metastases. The immediate-zoledronic acid group reported 3 contralateral breast cancers, whereas the delayed-zoledronic acid group reported 6. DFS was significantly improved when zoledronic acid was used immediately. DFS was improved with zoledronic acid initiation in this group. As a result of a larger (non-significant) proportion of patients initiating delayed zoledronic acid treatment at diagnosis (70%) compared to those not initiating delayed zoledronic acid (55%), the DFS benefits might be underestimated by delayed zoledronic acid introduction. Additionally, tumor stage was associated with DFS in the delayed-zoledronic acid group and age. In exploratory analyses, immediate zoledronic acid was associated with a trend toward improved DFS in recently menopausal and truly postmenopausal patients. An exploratory analysis of women with established postmenopausal status showed that immediate zoledronic acid was associated with improved DFS and significantly improved OS compared to delayed zoledronic acid. In addition to improving bone health, zoledronic acid administration immediately may improve DFS compared with delayed administration [32-34].

Phase 3 of the AZURE trial randomized 3360 women to receive standard adjuvant systemic treatment alone (control group) or intravenous zoledronic acid 4 mg every 3 - 4 weeks for 6 doses, followed by 8 doses every three months, followed by 5 doses every six months, for a total of five years. DFS events did not differ between the two groups. Similarly, both groups experienced long-term survival, overall survival, and distant recurrences. As a first event, zoledronic acid reduced bone metastases (HR 0.78, 95% CI 0.63 - 0.96; p = as well as at any time during follow-up (HR 0.81, 95% CI 0.68 - 0.97; p = 0.022). There was no effect of estrogen receptor (ER) status on the effects of zoledronic acid on DFS. In contrast, zoledronic acid improved IDFS in individuals over 5 years post menopause at trial entry, but not in all other menopausal groups. A DFS improvement of around 5% at 5 years and an osteonecrosis of the jaw rate of 1 - 2% suggest a favorable risk-benefit ratio for postmenopausal women with stage II or III breast cancer. Unselected patients with early breast cancer should not receive adjuvant zoledronic acid, based on these data. Postmenopausal women with early breast cancer who receive adjuvant treatment may be able to benefit from zoledronic acid, according to these studies. Using bisphosphonates, including zoledronic acid, a meta-analysis of 18,766 women with a median follow-up of 5 years found that there was a significant decrease in recurrence distant recurrence and breast cancer mortality. However, bone recurrence was more significant [35]. It was not significant by bisphosphonate class, treatment schedule, estrogen receptor status, or nodes for bone recurrence, nor by age or menopausal status. Among non-breast cancer survivors, no differences were found. Fractures of the bone were reduced. The use of adjuvant bisphosphonates including zoledronic acid improved breast cancer survival and reduced breast cancer recurrence in the bone, but only in postmenopausal women (Figure 2).

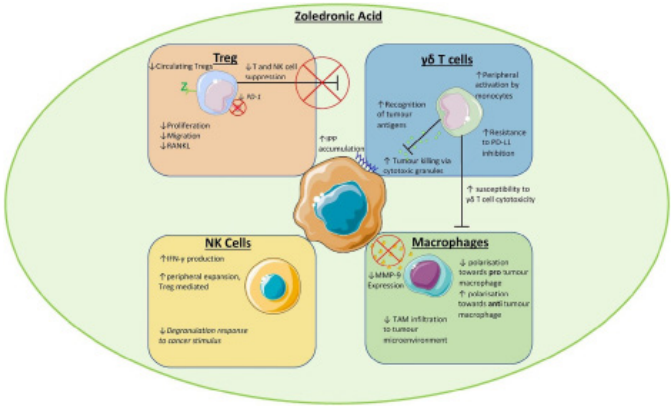

Figure 2: Effects of ZOL on the immune response to breast cancer [13].

Dosing based on biomarkers: The study of bone turnover biomarkers offers an avenue for evaluating skeletal metabolism in patients and the interactions between cancer and skeleton. A mutual effect between cancer and bone disrupts otherwise balanced activities, resulting in increased osteolysis and osteogenesis rates. The process releases biochemical markers that can be detected non-invasively in the blood or urine. There is significant evidence that tumor growth influences the rate of bone turnover based on biochemical markers of bone metabolism [36]. In addition to collagen peptides broken from osteolysis, there are also terminal peptides cleaved from procollagen before it is incorporated into newly synthesized bone matrix, such as amino [N]- and carboxy [C]-terminal cross-linked telopeptides [NTX and CTX], and peptides cleaved from procollagen before it is incorporated. In contrast, serum bone-specific alkaline phosphatase (bone ALP) and PINP are related to ongoing osteolysis, whereas serum CTX and urinary NTX are related to ongoing osteogenesis. In addition to osteolysis, osteocalcin also plays a role in osteogenesis. Generally, bone metabolism biochemical markers are related to osteolysis and osteogenesis rates. The variation in bone markers is not disease-specific and does not depend on the cause of the alteration in skeletal metabolism [2]. Biochemical markers of metabolism may not be able to predict a particular lesion site on the whole. Bone markers could be useful in identifying patients at high risk of bone metastasis or progression of bone lesions, according to emerging evidence. Clinical trials are necessary to determine the true value of bone metabolism biochemical markers [37, 38].

Challenges for Future Research

Several clinical trials are investigating zoledronic acid's anti-tumor effects as adjuvant or neoadjuvant therapy for breast cancer. A primary objective of this study is to compare the efficacy of zoledronic acid versus clodronate or ibandronate in treating women who have undergone surgery for breast cancer stage I, stage II, or stage III. For the first 5 years, DFS and OS are assessed every 6 months, then every year until death or recurrence. A total of 5400 patients were expected to enroll in the study. Both SUCCESS A and C study is an open-label, randomized, two-factor, phase III study for breast cancer patients at high risk (stage N1, or T2–T4, or grade 3, or age >35 years), or hormone receptor negative. As per our study from different papers, we aimed to determine the predictive power of zoledronic acid treatment on the prevalence of CTCs five years after primary diagnosis, in addition to other well-known predictors [39, 40]. As part of the adjuvant chemotherapy treatment, patients received three cycles of FEC followed by 3 cycles each of docetaxel or gemcitabine-docetaxel. Furthermore, zoledronic acid treatment was randomized to 3 years versus 5 years. In some studies, between 2015-2023 SABCS, zoledronic acid treatment duration did not affect the prevalence of CTCs five years after primary diagnosis. Even after adjuvant therapy, CTCs may remain, according to the same results. Patients with HER2-positive tumors seem to have a higher rate of CTCs immediately after chemotherapy than those with other molecular subtypes. There may be other trials in this setting that provide additional information on CTCs' predictive role in bisphosphonate treatment [41]. Natan compares neoadjuvant therapy with and without zoledronic acid, and this is a study we are closely following. In this phase III study, patients with histological tumor residuals following preoperative anthracycline and taxane-containing chemotherapy for primary breast cancer will be compared with those receiving no postoperative treatment with zoledronic acid [42, 43]. Five-year event-free survival from the time of postoperative treatment is the primary endpoint. This paper provides important information about how zoledronic acid affects postmenopausal breast cancer patients. More studies should be designed in this population to explore appropriate dosing and duration of zoledronic acid therapy, and to better understand its mechanisms [12, 44].

Conclusion

The anti-important effects of zoledronic acid are in addition to its effects on BMD and bone remodeling. Patients with post-menopausal breast cancer face several factors, including a low estrogen environment caused by its dosing schedule. Several studies suggest that effects of estrogen on the bone microenvironment may play a substantial role in determining who may benefit most from adjuvant zoledronic acid therapy. Ongoing analyses of different databases may offer additional insights into the possible effects on BMD and bone remodeling outcomes with zoledronic acid. Overall, current clinical data suggest that both estrogen deprivation and reduction of bone turnover-derived growth factors in the bone marrow microenvironment are needed for sufficient suppression of dormant micrometastases in patients with early stage, hormone-receptor-positive breast cancer. The administration of this agent four to six times a year can improve the prognosis of cancer patients, whereas a low dose a week may have stronger antitumor effects. These hypotheses, however, need to be tested in clinical trials.

Acknowledgements

None.

Conflict of Interest

None.

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