Efficacy of zoledronic acid in postmenopausal women with early breast cancer receiving adjuvant letrozole: 36-month results of the ZO-FAST Study

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Background: Aromatase inhibitors (AIs) are accepted adjuvant endocrine therapy in postmenopausal women (PMW) with hormone receptor-positive early breast cancer (EBC) with efficacy superior to tamoxifen. However, increased bone loss is associated with AIs.

Patients and methods: PMW with EBC receiving letrozole (2.5 mg/day for 5 years) were randomly assigned to immediate zoledronic acid (ZOL; 4 mg every 6 months) or delayed ZOL (initiated only for fracture or high risk thereof).

Results: Patients (N = 1065) had a median age of 58 years; 54% had received prior adjuvant chemotherapy. At 36 months, mean change in L2-L4 bone mineral density (BMD) was +4.39% for immediate versus 2.4% for delayed ZOL (P < 0.0001). Between-group differences were 5.27% at 12 months, 7.94% at 24 months, and 9.29% at 36 months (P < 0.0001 for all). At 36 months, the immediate-ZOL group had a significant 41% relative risk reduction for disease-free survival (DFS) events (P = 0.0314). Adverse events are consistent with the known safety profiles of the study drugs.

Conclusions: At 36 months, immediate ZOL was more effective in preserving BMD during letrozole therapy. Immediate versus delayed ZOL led to significantly improved DFS. Benefits are observed in the context of a favorable, well-established safety profile for letrozole and ZOL.

Key words: adjuvant therapy, anticancer, aromatase inhibitor, bone loss, breast cancer, survival, zoledronic acid

introduction

Aromatase inhibitors (AIs) are accepted adjuvant endocrine therapy in postmenopausal women (PMW) with hormone receptor-positive early breast cancer (EBC) with efficacy superior to tamoxifen (TAM) [1–3], but with increased bone loss [4]. TAM antagonizes tumor-cell estrogen receptors (ERs), whereas AIs block peripheral-tissue estrogen synthesis. In the Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial, 5-year fracture risk with anastrozole was 44% higher than that with TAM [2]. Similar fracture risk increases with letrozole or exemestane versus TAM for EBC in PMW were reported in the Breast International Group 1-98 and Intergroup Exemestane Study studies, respectively [3, 5].

Clinical trials have assessed bisphosphonates for preventing aromatase inhibitor-associated bone loss (AIBL) [e.g. Arimidex-Bondronat, Study of Anastrozole with the Bisphosphonate Risedronate, Zometa-Femara Adjuvant Synergy Trials (Z-FAST, ZO-FAST and E-ZO-FAST)], and strong evidence [mostly from zoledronic acid (ZOL) trials] shows that AIBL is preventable and manageable with bisphosphonates [6–8]. In other adjuvant EBC studies, ZOL was associated with significant improvements in cancer outcomes. In the landmark Austrian Breast and Colorectal Cancer Study Group trial 12 (ABCSG-12 trial) (N = 1803), ZOL improved disease-free survival (DFS) by 36% (P = 0.01) in premenopausal women with endocrine-responsive EBC [9], with reductions in contralateral breast cancer, secondary malignancies, death, and locoregional and distant recurrence. Further, in the bone mineral density (BMD) substudy, ZOL prevented the profound bone loss observed when goserelin was combined with TAM or anastrozole [10, 11].

Consistent with the efficacy of ZOL for preserving BMD, immediate ZOL significantly improved the percentage change in lumbar spine (LS) BMD from baseline to 12 months in the previously reported primary end point of the ZO-FAST [12]. We report here the BMD, DFS, and safety results of ZO-FAST after 36 months’ median follow-up.
methods

study patients

Enrollment criteria, design, and ethics review of ZO-FAST were described previously [12]. Briefly, PMW and recently menopausal women (because of chemotherapy or ovarian suppression for treatment of EBC) with ER+ and/or progesterone receptor-positive, stage I–IIIa EBC and baseline LS and total hip BMD T-score $\geq -2.0$ were enrolled.

study design

ZO-FAST is an open-label, multicenter, randomized study. All patients received adjuvant oral daily letrozole (2.5 mg) for 5 years and were randomly assigned to receive immediate or delayed ZOL (4 mg via 15-min infusion every 6 months) for 5 years. Immediate-ZOL patients received ZOL immediately after randomization; delayed-ZOL patients received ZOL only if their T-score fell below $-2.0$, after a nontraumatic clinical fracture, or if an asymptomatic fracture was detected by spinal X-ray at the 36-month or more of ZOL. Patients received daily supplements containing calcium (500 mg) and vitamin D (400–800 IU). Patients were stratified by adjuvant chemotherapy (yes/no), baseline T-score ($-2.0$ to $-1.0$ or above $-1.0$), and menopausal stage (recently menopausal or established postmenopausal).

patient evaluations

The primary end point was percentage change in LS (L2-L4) BMD at 12 months for immediate- versus delayed-ZOL patients. Secondary end points included percentage change in total hip BMD at each assessment, 3-year fracture incidence, time to disease recurrence (local relapse or distant metastasis), overall survival, and safety. DFS was defined as a period free from disease recurrence or death from any cause. Neither contralateral breast cancer nor second primary tumors were included in the DFS analysis. For the safety population, patients were included in the immediate-ZOL group if they received the first dose of ZOL within the first 4 weeks on study; otherwise, they were included in the delayed-ZOL group. Serious adverse events (SAEs) were defined according to MedWatch criteria [13]. Patients who discontinued early were assessed 4 weeks after stopping treatment and followed up for disease recurrence or death at 6-month intervals until 5 years after final patient random assignment. All suspected cases of osteonecrosis of the jaw (ONJ) were reported as SAEs and referred for each comparison. Among patients with baseline L2-L4 T-scores between $-2.0$ and $-1.0$, many immediate-ZOL patients but relatively few delayed-ZOL patients transitioned to normal BMD (T-score $> -1.0$; Figure 2B). Conversely, relatively few immediate-ZOL patients (51.4% at each time point) but more delayed-ZOL patients (~14%) at month 36 had severe osteopenia/osteoporosis (T-score $< -2.0$), despite ZOL initiation in some delayed-ZOL patients. Between-group differences were statistically significant ($P < 0.001$) at each postbaseline assessment. Similarly, among patients with normal baseline BMD, more maintained T-scores $> -1.0$ at 36 months in the immediate- versus delayed-ZOL groups [192/315 (61%) versus 142/324 (43.8%) assessable patients, respectively], whereas more delayed-ZOL patients had T-scores $\leq -1.0$ (17.3%, versus 1.9% for immediate ZOL; $P < 0.001$ for BMD-shift differences), and two delayed-ZOL but no immediate-ZOL patients had T-scores $< -2.0$.

In the safety analysis, 26 (5.0%) immediate-ZOL patients and 32 (6.0%) delayed-ZOL patients experienced fractures ($P = 0.502$, Fisher’s exact test). Clinical fractures occurred in 24 (4.6%) immediate-ZOL patients and 26 (4.9%) delayed-ZOL patients. Among patients with baseline and 36-month
assessments (339 immediate and 344 delayed ZOL), new radiologically detected fractures were recorded for only three immediate-ZOL patients (0.9%): two were mild (20%–24% reduction in vertebral height), and one was considered moderate (25%–40% reduction in vertebral height). In contrast, eight delayed-ZOL patients (2.3%) had radiologically detected fractures not present at baseline: one severe (>40% reduction in vertebral height), five moderate, and two mild.

disease recurrence and survival

In the intent-to-treat population, 506/532 immediate-ZOL patients and 489/532 delayed-ZOL patients were disease free and alive, for an absolute DFS difference of 3.2% between treatment arms. This difference correlates with a significant 41% relative reduction in the risk of having a DFS event (i.e., disease recurrence or death) for immediate versus delayed ZOL (HR = 0.588; 95% CI = 0.361–0.959; log-rank $P = 0.0314$; Figure 3). When delayed-ZOL patients ($n = 110$) were censored at the first ZOL dose, the reduced risk of DFS events for immediate versus delayed ZOL (HR = 0.584; 95% CI = 0.352–0.968; log-rank $P = 0.0347$) was similar to that for the noncensored analyses.

The effects of ZOL were not limited to bone: immediate-ZOL patients had fewer local [2 (0.4%) versus 10 (1.9%) for delayed ZOL] and distant recurrences [20 (3.8%) versus 30 (5.6%) for delayed ZOL; Figure 3; supplemental Table S2, available at Annals of Oncology online]. Notably, only 9 (1.7%) immediate-ZOL patients versus 17 (3.2%) delayed-ZOL patients developed bone metastases.

safety

Adverse events were similar between groups (Table 1); however, immediate-ZOL patients experienced slightly more influenza-like symptoms, including bone pain (15.3% versus 10.1%) and headaches (12.4% versus 9.5%), and more pyrexia (14.9% versus 2.8%) than delayed-ZOL patients. Influenza-like symptoms are associated with an acute-phase reaction, most common after the first ZOL infusion then occurring less frequently after subsequent infusions [14]. SAEs occurred in 15.8% of immediate-ZOL patients and in 14.2% of delayed-ZOL patients. Adverse events resulting in study withdrawal occurred in 8.6% of immediate-ZOL patients and 7.5% of delayed-ZOL patients.

Regular renal function monitoring throughout the trial revealed few renal adverse events. Although no study drug-related renal failure was reported, the number of patients with renal failure/impairment was higher in delayed-ZOL (0.6%) versus immediate-ZOL patients (0.2%). Overall, four patients experienced renal failure/impairment (three delayed-ZOL patients, none of whom had initiated ZOL beforehand; one immediate-ZOL patient).

osteonecrosis of the jaw

Two immediate-ZOL patients reported potential ONJ events that were subsequently confirmed by the independent ONJ adjudication committee (0.4% incidence; total ZOL doses: two and five). The first patient experienced ONJ of the left mandible after receiving two doses of ZOL; no prior invasive dental procedures or trauma were reported. The second patient had
a complex dental history and underwent a difficult dental extraction with evulsions of small bone pieces and delayed healing 1 year before experiencing a new dental bone expulsion at the site of the previous extraction, which was subsequently adjudicated as ONJ. Further follow-up data are limited because these patients went off study after their events.

**discussion**

In this 36-month analysis of ZO-FAST, the improvements reported for immediate versus delayed ZOL for the primary trial end point (12-month L2-L4 BMD) [12] were maintained, and BMD continued to increase. Few patients had fractures (5% immediate- versus 6% delayed-ZOL patients; \(P = 0.5\)), although the trial was not powered for this end point. Use of ‘rescue’ ZOL after patients’ BMD T-score decreased below \(-2.0\) may have protected delayed-ZOL patients from further BMD decline, potentially preventing additional fractures. Indeed, 110 (21%) delayed-ZOL patients initiated ZOL on study.

After 36 months, shifts from normal BMD (T-score \(> -1.0\) but \(< -2.0\)) to osteopenic/osteoporotic BMD (T-score \(\leq -1.0\); 1.9% for immediate, 17.3% for delayed ZOL), and from osteopenic BMD to severe osteopenia/osteoporosis (T-score \(\leq -2.0\); 0.7% for immediate, 13.7% for delayed ZOL) were more common in delayed- versus immediate-ZOL patients (\(P < 0.001\) for each distribution). Osteoporosis studies in PMW have shown that a premature decrease in BMD, as observed in

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**Figure 2.** Changes in bone mineral density (BMD) and T-score categories throughout the Zometa-Femara Adjuvant Synergy Trial study. (A) Mean percentage changes in lumbar spine and total hip BMD at 12, 24, and 36 months in women with early-stage breast cancer receiving immediate or delayed zoledronic acid (ZOL) in patients with BMD data at baseline. \(P < 0.0001\) for between-group comparisons at all time points. (B) For each postbaseline time point, between-group differences in the T-score category distribution were statistically significant (\(P < 0.001\)).
delayed-ZOL patients, can significantly increase long-term fracture risk [15, 16]. Therefore, longer term follow-up may be required to ascertain the true fracture ramifications of AIBL and of delaying ZOL treatment.

In addition to BMD differences, the current 36-month analysis revealed significant differences in clinical outcomes based on secondary end points. Patients who received adjuvant letrozole plus immediate ZOL had a statistically significant 41% relative reduction in the risk of DFS events (log-rank \( P = 0.0314 \)), consistent with anticancer effects. Osteolysis releases various bone matrix-derived growth factors that can stimulate adjacent tumor cells to proliferate and release their own growth factors, which—in turn—lead to further osteoclast activation. This so-called 'vicious cycle' can be stopped by ZOL, which inhibits osteoclast-mediated osteolysis. The bone marrow microenvironment is rich in growth factors and can act as a sanctuary for tumor stem cells [17]; ZOL can reduce the release of growth factors from the bone matrix, thereby potentially reducing the risk that micrometastatic disease will progress to clinically relevant metastatic disease [18]. Moreover, ZOL may have direct anticancer effects [18]. Reductions in bone marrow-disseminated tumor cells with adjuvant ZOL plus chemotherapy versus baseline or chemotherapy alone [19–22] may reduce the potential for tumor cells in bone to become radiologically detectible bone metastases or to disseminate to other sites, thereby improving survival [23].

The DFS benefits detected as secondary end points in PMW in this study are consistent with those reported for the primary end point in premenopausal patients in the ABCSG-12 trial [9] and with the significant reduction in disease recurrence with immediate versus delayed ZOL in the pooled Z-FAST/ZO-FAST 12-month analysis (\( P = 0.040 \)) [24]. The clinical manifestations of the anticancer and antimetastatic effects of ZOL are supported by numerous preclinical investigations showing that ZOL can induce tumor-cell apoptosis, inhibit tumor-cell invasion/migration, reduce angiogenesis, activate anticancer immune responses, and synergize with chemotherapy agents [18, 25]. In pilot studies of EBC patients receiving neo-adjuvant therapy, ZOL reduced the prevalence of detectable disseminated tumor cells in the bone marrow, which

Table 1. Adverse events occurring in >5% of patients in the safety population

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Immediate ZOL (n = 524)</th>
<th>Delayed ZOL (n = 536)</th>
</tr>
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<tbody>
<tr>
<td>Arthralgia</td>
<td>221 (42.2)</td>
<td>218 (40.7)</td>
</tr>
<tr>
<td>Hot flashes</td>
<td>135 (25.8)</td>
<td>150 (28.0)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>84 (16.0)</td>
<td>81 (15.1)</td>
</tr>
<tr>
<td>Bone pain</td>
<td>80 (15.3)</td>
<td>54 (10.1)</td>
</tr>
<tr>
<td>Back pain</td>
<td>55 (10.5)</td>
<td>61 (11.4)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>78 (14.9)</td>
<td>65 (12.4)</td>
</tr>
<tr>
<td>Headache</td>
<td>63 (12.4)</td>
<td>51 (9.5)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>62 (11.8)</td>
<td>65 (12.1)</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>57 (10.9)</td>
<td>63 (11.8)</td>
</tr>
<tr>
<td>Nausea</td>
<td>46 (8.8)</td>
<td>42 (7.8)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>40 (7.6)</td>
<td>35 (6.5)</td>
</tr>
<tr>
<td>Weight increase</td>
<td>39 (7.4)</td>
<td>47 (8.8)</td>
</tr>
<tr>
<td>Cough</td>
<td>33 (6.3)</td>
<td>33 (6.2)</td>
</tr>
<tr>
<td>Lymphedema</td>
<td>34 (6.5)</td>
<td>29 (5.4)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>31 (5.9)</td>
<td>37 (6.9)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>31 (5.9)</td>
<td>20 (3.7)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>29 (5.5)</td>
<td>38 (7.1)</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>26 (5.0)</td>
<td>31 (5.8)</td>
</tr>
<tr>
<td>Osteoarthritis</td>
<td>30 (5.7)</td>
<td>18 (3.4)</td>
</tr>
<tr>
<td>Depression</td>
<td>25 (4.8)</td>
<td>35 (6.5)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>21 (4.0)</td>
<td>32 (6.0)</td>
</tr>
<tr>
<td>Constipation</td>
<td>17 (3.2)</td>
<td>28 (5.2)</td>
</tr>
</tbody>
</table>

ZOL, zoledronic acid.

Figure 3. Kaplan–Meier plots of disease-free survival in women with early-stage breast cancer receiving immediate or delayed zoledronic acid. \( P \) value is for stratified intergroup comparisons at 36 months. CI, confidence interval; ZOL, zoledronic acid.
might result in lower rates of disease recurrence [20, 26]. However, DFS results in PMW require confirmation from large, prospective, randomized, controlled studies designed to assess the effect of ZOL on DFS and overall survival, such as the ongoing AZURE, SUCCESS, and NATAN studies. The AZURE study has already yielded promising early evidence of anticancer effects with ZOL in its neo-adjuvant substudy [27]. In that 205-patient subset, adding ZOL was associated with a 44% reduction in residual tumor volume ($P = 0.006$) and an approximately two-fold improvement in complete pathologic response versus chemotherapy alone ($P = 0.146$) [26].

Limitations of the current study include the lack of standardized and preplanned tests to screen for disease progression, such as those implemented in ABCSG-12, and the use of ZOL in the control arm (delayed ZOL), which could confound between-group comparisons. However, when delayed-ZOL patients who received ZOL ($n = 110$) were censored at the first ZOL dose, the DFS results were similar to those of the censored analyses. At this point, it is unknown to what extent ZOL initiation may have affected outcomes in the delayed-ZOL group.

In ZO-FAST, ZOL was generally well tolerated. Acute-phase influenza-like reactions were manageable, there were minimal renal adverse events, and there were only two cases of ONJ (0.4% of patients). There were no confirmed ONJ cases in ABCSG-12 or in the 36-month and 61-month analyses of Z-FAST [28, 29]. This low incidence is as expected with early-stage cancers, infrequent ZOL dosing, and implementation of the preventive oral health practices in patients recommended by Weitzman et al. [30].

The 36-month analysis of ZO-FAST shows that the BMD benefits of immediate ZOL initiation continue and appear to increase over time. Moreover, consistent with recent reports in premenopausal women with EBC [9], adding ZOL to adjuvant endocrine therapy in PMW resulted in significant improvements in DFS. Longer follow-up will provide additional information on preventing fracture and prolonging DFS in PMW receiving immediate versus delayed ZOL combined with adjuvant letrozole therapy for EBC.

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**references**

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