Daily oral ibandronate with adjuvant endocrine therapy in postmenopausal women with estrogen receptor-positive breast cancer: editorial commentary

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Metastasis is a complex multistep process that depends on a range of biological characteristics within the primary tumor as well as the host response and interactions with the microenvironment within distant metastatic sites such as the bone marrow microenvironment (1). Tumors such as breast cancer have a particular predilection to spread to bone with disseminated cells able to survive in the circulation and colonize metastatic niches within the bone marrow microenvironment. Here they are able to enter a state of dormancy where they may survive for many years and remain sub-clinical before awakening, starting to proliferate and establishing overt metastases either within bone or at other sites such as liver, lung and brain. Bone targeted agents such as the bisphosphonates, which have profound effects on bone cell function and modify the bone microenvironment, have been studied in numerous randomized clinical trials for more than two decades. However, variable results have been observed and the use of adjuvant bisphosphonates in women with early breast cancer remained an area of controversy (2).

The Early Breast Cancer Clinical Trials Collaborative Group (EBCTCG) published a large, comprehensive individual patient meta-analysis of all available data from randomized trials that appeared to confirm the hypothesis identified in several individual trials (3,4) that efficacy was limited to postmenopausal women—either through natural ageing or the use of ovarian function suppression (5). In this sub-population, clinically and statistically significant benefits were seen with prevention of around one in four recurrences of disease in bone and one in six breast cancer deaths, while no benefits were seen in premenopausal women. Indirect comparisons between trials testing intravenous zoledronate (various schedules), daily oral clodronate and daily oral ibandronate suggested that bisphosphonates were effective as a class of agents despite differences in molecular action. This was supported by a large randomized trial of these three agents which showed no difference in outcomes with the three different treatment strategies (6).

The TEAM-IIB trial reported by Vliek and colleagues evaluated oral ibandronate 50 mg daily for three years in a randomized, open label trial conducted in 1,116 women with estrogen receptor positive (ER+) stages I-III early breast cancer (7). Early analyses, performed at a median of three years follow-up corresponding with the end of treatment suggested benefit with fewer recurrences in bone and improved disease-free survival (DFS) in the ibandronate treated patients. However, the analyses reported in this manuscript after a median follow-up of 8.5 years failed to show any long-term benefits from oral ibandronate in this population of patients and the authors conclude that daily oral ibandronate is not an effective treatment in post-menopausal ER+ breast cancer.

There are some important design features that may explain the lack of efficacy observed. Firstly, oral ibandronate was started after (neo)adjuvant chemotherapy [received by (56%)] and loco-regional treatments had been completed resulting in considerable delay in the initiation of treatment in the majority of patients. This is different to most of the trials included in the EBCTCG meta-analysis where adjuvant bisphosphonates were initiated alongside systemic chemotherapy. Colonization of the bone marrow occurs early in patients destined to develop disease relapse and it may be important that the microenvironment is modified early before disseminated tumor cells (DTCs) have had a chance to become established within the bone marrow niches and tumor dormancy has developed. Unfortunately, the forest plot of sub-group analyses does not include early (no chemotherapy) versus delayed (chemotherapy administered) initiation of ibandronate.

Secondly, ibandronate was continued for three years and the effects on bone cell function could be expected to wane during year four. In contrast, zoledronate has a longer duration of action with effects on bone cell function still evident many years after administration (8). The slow off-set of effects with zoledronate or the need to continue administration beyond 3 years for long term benefits may be necessary. Only the SUCCESS-B trial has investigated duration of treatment; disease outcomes and persistence of DTCs with adjuvant zoledronate for three or five years were compared. No differences in efficacy were seen although the trial was under-powered to reliably evaluate non-inferiority of the shorter duration regimen (9). Additionally, zoledronate was not initiated until adjuvant chemotherapy had been completed, potentially affecting the impact of both treatment schedules on disease outcomes.

Thirdly, the sample size in the TEAM-IIB trial was amended due to slow accrual from 2,058 to 1,116 patients resulting in reduced power to identify any likely differences in outcomes, especially when one takes into account that 30% of patients in the ibandronate arm discontinued treatment early including around 10% within the first 6 months. Finally, the primary endpoint of DFS includes non-breast cancer events such as deaths from other causes and development of a new second primary. It is of interest that the relapse free interval curves continue to show a difference in favor, albeit not significant, of the ibandronate treated patients whereas the DFS and overall survival curves merge and cross at around 7–8 years. More meaningful endpoints, particularly in an older population of patients at significant risk for non-breast cancer events are breast cancer recurrence and breast cancer deaths as used by the EBCTCG in all their analyses.

The patients selected for treatment in the TEAM-IIB trial were consistent with current clinical guidelines (10,11). However, recent data suggest the use of a fluorescent in-situ hybridization (FISH) test to determine levels of expression of the predictive biomarker MAF identifies patients most likely to benefit from zoledronate (12) or oral clodronate (13) with benefits restricted to the 80% of patients found to have normal levels of MAF (MAF-negative), while the remaining 20% of patients with tumors that have amplified expression of MAF (MAF positive) gain no benefit and may be at increased risk of developing life-threatening extra-skeletal metastases. It would be intriguing to investigate outcomes in the TEAM-IIB study according to MAF status.

So, how should the results of the TEAM-IIB study influence clinical practice? Oral ibandronate is not recommended by North American guidelines as the agent is not approved for any indication in the United States (10). However, current clinical guidelines in Europe include daily oral ibandronate as an alternative treatment option to intravenous zoledronate or daily oral clodronate (11). Because of the relatively high rate of gastrointestinal adverse events and the complexity of adhering to daily oral ibandronate requiring administration on an empty stomach, with the need for an upright posture to speed up passage through the esophagus and no oral intake, other than water, for an hour after administration, most clinicians initiate treatment with intravenous zoledronate and offer patients the option to transition to oral therapy after completion of (neo)adjuvant chemotherapy. As in the TEAM-IIB study, around 1 in 6 patients evaluated in routine clinical practice discontinued oral ibandronate because of adverse events, typically within the first six months (14). It is important that such patients are offered the option to resume/initiate intravenous zoledronate. The EBCTCG is performing an update of the bisphosphonate meta-analysis and will look to address the potential importance of when adjuvant bisphosphonates are initiated as well as treatment duration. Pending this, intravenous zoledronate for 3–5 years provides the simplest option that ensures compliance and the opportunity to gain the benefits of treatment.

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Footnote

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Ethical Statement: The author is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Clézardin P, Coleman R, Puppo M, et al. Bone metastasis: mechanisms, therapies, and biomarkers. Physiol Rev 2021;101:797-855.
2. Coleman R. Bone-Targeted Agents and Metastasis Prevention. Cancers (Basel) 2022;14:3640.
3. Coleman RE, Marshall H, Cameron D, et al. Breast-cancer adjuvant therapy with zoledronic acid. N Engl J Med 2011;365:1396-405.
4. Gnant M, Mlineritsch B, Stoeger H, 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 2011;12:631-41.
5. Adjuvant bisphosphonate treatment in early breast cancer: meta-analyses of individual patient data from randomised trials. Lancet 2015;386:1353-61.
6. Gralow JR, Barlow WE, Paterson AHG, et al. Phase III Randomized Trial of Bisphosphonates as Adjuvant Therapy in Breast Cancer: S0307. J Natl Cancer Inst 2020;112:698-707.
7. Vliek SB, Noordhoek I, Meershoek-Klein Kranenbarg E, et al. Daily Oral Ibandronate With Adjuvant Endocrine Therapy in Postmenopausal Women With Estrogen Receptor-Positive Breast Cancer (BOOG 2006-04): Randomized Phase III TEAM-IIB Trial. J Clin Oncol 2022;40:2934-45.
8. Brown JE, Ellis SP, Lester JE, et al. Prolonged efficacy of a single dose of the bisphosphonate zoledronic acid. Clin Cancer Res 2007;13:5406-10.
9. Friedl TWP, Fehm T, Müller V, et al. Prognosis of Patients With Early Breast Cancer Receiving 5 Years vs 2 Years of Adjuvant Bisphosphonate Treatment: A Phase 3 Randomized Clinical Trial. JAMA Oncol 2021;7:1149-57.
10. Eisen A, Somerfield MR, Accordino MK, et al. Use of Adjuvant Bisphosphonates and Other Bone-Modifying Agents in Breast Cancer: ASCO-OH (CCO) Guideline Update. J Clin Oncol 2022;40:787-800.
11. Coleman R, Hadji P, Body JJ, et al. Bone health in cancer: ESMO Clinical Practice Guidelines. Ann Oncol 2020;31:1650-63.
12. Coleman R, Hall A, Albanell J, et al. Effect of MAF amplification on treatment outcomes with adjuvant zoledronic acid in early breast cancer: a secondary analysis of the international, open-label, randomised, controlled, phase 3 AZURE (BIG 01/04) trial. Lancet Oncol 2017;18:1543-52.
13. Paterson AHG, Lucas PC, Anderson SJ, et al. MAF Amplification and Adjuvant Clodronate Outcomes in Early-Stage Breast Cancer in NSABP B-34 and Potential Impact on Clinical Practice. JNCI Cancer Spectr 2021;5:pkab054.
14. Wilson C, Martin C, Winter MC. Compliance and patient reported toxicity from oral adjuvant bisphosphonates in patients with early breast cancer. A cross sectional study. J Bone Oncol 2019;15:100226.

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