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The efficacy of zoledronic acid in breast cancer adjuvant therapy: A meta-analysis of randomised controlled trials

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ABSTRACT

Background: The effect of zoledronic acid in breast cancer adjuvant therapy concerning improvement of patient survival has yet to be confirmed. We performed a meta-analysis of published and unpublished randomised controlled trials with the aim of accurate evaluation between clinical outcome and the association of the addition of zoledronic acid to adjuvant therapy.

Methods: We searched PubMed (from 1966 to present) and online abstracts from the proceeding Annual Meetings of the American Society of Clinical Oncology (ASCO) (years 1992–2010) and online abstracts from San Antonio Breast Cancer Symposium (years 2004–2010). A total of five eligible studies including 3676 subjects and 3678 controls met our search criteria and were evaluated. Random and fixed-effects meta-analytical models were used where indicated, and between-study heterogeneity was assessed. The primary study end-points were the disease free survival (DFS). Secondary end-points were overall survival (OS), distant or loco-regional recurrence free survival and bone metastasis free survival.

Findings: Compared with the control arm, adjuvant breast cancer treatment with zoledronic acid did not significantly improve overall survival, disease free survival, bone metastasis free survival, distant and locoregional recurrence free survival. However, in the postmenopausal subgroup, the addition of zoledronic acid to standard therapy could significantly improve DFS (relative risk (RR) = 0.763, 95% confidence interval (CI) 0.658–0.884, $p < 0.001$) and reduce the risk of distant (RR = 0.744, 95% CI 0.611–0.906, $p = 0.003$) and locoregional recurrence (RR = 0.508, 95% CI 0.340–0.760, $p = 0.001$).

Interpretation: Adjuvant zoledronic acid did not significantly improve the prognosis of breast cancer patients. Due to the highly variable definitions of menopause utilised in different studies, we hypothesise that zoledronic acid may have a potential effect on postmenopausal patients. Additional studies are needed to evaluate the value of adjuvant treatment of zoledronic acid in premenopausal counterparts, differing disease stages and various pathological types of breast cancer.

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1. Introduction

Breast cancer is the most common cancer in women and remains the second leading cause of cancer death among women worldwide.[1] Although major advances in cancer and adjuvant therapies for breast cancer have been achieved over the past 60 years, a substantial number of patients experience disease relapse. As the disease progresses, approximately 70% of all metastatic breast cancer patients develop bone metastasis, which in turn increases the risk of fracture through osteoclast-mediated destruction of the surrounding bone,[2] and is the cause of considerable morbidity. The median survival after first relapse in the bone is 20 months.[3] In addition to the effect of cancer on bone metabolism, cancer treatment induced bone loss (CTIBL) is a critical problem that includes hypoestrogenism secondary to gonadotropin-releasing hormone antagonists in premenopausal women or aromatase inhibitors in postmenopausal women.[4–7] Therefore, the treatment of both bone loss and bone metastasis is of great importance in order to improve quality of life and extend survival for breast cancer patients.

Bisphosphonates (BPs), as potent inhibitors of osteoclast-mediated bone resorption, have demonstrated proven clinical utility for the treatment of both postmenopausal osteoporosis[8] and bone metastasis.[9] The third-generation bisphosphonate zoledronic acid, characterised by an imidazole ring containing two nitrogen atoms, is the most potent of the available nitrogen containing BPs (N-BPs).[10] The Health Outcomes and Reduced Incidence with Zoledronic Acid One Yearly Pivotal Fracture Trial (HORIZON) showed that a single infusion of intravenous zoledronic acid could significantly improve bone density and reduce the risk of bone fractures in postmenopausal women with osteoporosis.[11] Additionally, multiple clinical trials have demonstrated that zoledronic acid effectively prevents CTIBL and increases bone mineral density (BMD) above baseline levels.[12–15]

Interestingly, the true effect of zoledronic acid seems to have a wider spectrum. Preclinical data have revealed a direct anti-tumour role for zoledronic acid which may act through the inhibition of tumour cell adhesion, invasion and proliferation as well as acting to induce apoptosis in multiple human tumour cell lines.[16] However, no such effect has been observed in thousands of breast cancer patients. Recently, several randomised controlled trials[17–19] have been reported on adjuvant zoledronic acid treatment, although the results were somewhat controversial. The Austrian Breast and Colorectal Cancer Study Group Trial 12 (ABCSG 12) and Zometa-Femara Adjuvant Synergy Trial (ZO-FAST) were in concordance regarding the addition of zoledronic acid to adjuvant endocrine therapy, which significantly improved the disease-free survival (DFS) of breast cancer patients,[20] whereas Coleman and colleagues[18,20] reported on the AZURE (Adjuvant Treatment with Zoledronic Acid in Stage II/III Breast Cancer) trial at the 33th SABCS (San Antonio Breast Cancer Symposium) last December that adjuvant use of zoledronic acid failed to improve DFS. In the neoadjuvant subgroup of the AZURE, the addition of zoledronic acid to neoadjuvant chemotherapy could significantly reduce the residual invasive tumour size at surgery ($p = 0.006$); however, there was no significant difference in pathological complete response (pCR) ($p = 0.146$).[21] Thus, we performed a meta-analysis in order to obtain a more precise understanding of the role of zoledronic acid in the adjuvant therapy for breast cancer patients.

2. Methods

2.1. Publication search

The electronic database PubMed (from 1966 to the present) and online abstracts from the proceeding Annual Meetings of the American Society of Clinical Oncology (ASCO) (years 1992–2010) and online abstracts from SABCS (years 2004–2010) were searched by investigators. The following algorithm was used to perform the search: 'adjuvant', 'breast cancer', and 'zoledronic acid' or 'zometa'. The citation list associated with all the studies retrieved in the search was used to identify other potentially relevant publications. Review articles were also scanned to find additional eligible studies. The final search was updated on the 13th December, 2010. The search results were then screened according to the following inclusion criteria: (a) phase III prospective randomised trial, (b) zoledronic acid used in the adjuvant setting for breast cancer, (c) inclusion of sufficient data to allow for the estimation of a relative risk (RR) with a 95% confidence interval (95% confidence interval (CI)) of DFS and OS and (d) English language publications. If multiple publications of the same trial were retrieved, or if there was a case overlap between publications, only the most recent publication (the most informative) was included. Non-randomised studies were excluded, as were letters to the editor, reviews, abstracts containing insufficient detail to meet the inclusion criteria, articles published in a book and papers published in a language other than English.

2.2. Data extraction

The following data were collected from each of the included studies: first authors' surname, year of publications, number of patients randomly assigned and analysed per arm, menopausal status, the exact regimens used and the corresponding doses and schedules. We also recorded the median duration of follow-up. The outcome measures were based on the intention-to-treat analysis (ITT). Two of the authors of the present study (T.T.Y. and W.J.Y.) independently and carefully extracted the information indicated from all eligible publications. All discrepancies were addressed by a third author (J.S.L.) until a consensus was achieved on every single item. The primary study end-points were the DFS. Secondary end-points were OS, distant or loco-regional recurrence free survival and bone metastasis free survival.

2.3. Statistical analysis

Relative risk with a 95% confidence interval (95% CI) was used to estimate the value of zoledronic acid in breast cancer adjuvant therapy. The heterogeneity assumption was calculated using the chi-square based Q-test ($p < 0.10$ was considered significant)[22] or the I-square statistic to examine the extent of between-study heterogeneity (considered large for I^2 values