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Review Article

Are adjuvant bisphosphonates now standard of care of women with early stage breast cancer? A debate from the Canadian Bone and the Oncologist New Updates meeting

Carmel Jacobs [a,*], Eitan Amir [b], Alexander Paterson [c], Xiaofu Zhu [a], Mark Clemons [a]

[a] The Ottawa Hospital Cancer Center & University of Ottawa, Ottawa, Ontario, Canada
[b] Division of Medical Oncology, Princess Margaret Hospital, Toronto, Canada
[c] Tom Baker Cancer Centre and University of Calgary, Alberta, Canada

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ABSTRACT

The 9th Bone and the Oncologist New Updates conference was held in Ottawa, Canada during 2014. This annual meeting focuses on innovative research into the mechanisms and consequences of treatment-induced and metastatic bone disease. Given the recent presentation of the Oxford overview's "Effects of bisphosphonate treatment on recurrence and cause-specific mortality in women with early breast cancer: A meta-analysis of individual patient data from randomized trials" at the San Antonio Breast Cancer Symposium, a debate as to the pro's and con's of adjuvant bisphosphonate use in early stage breast cancer was undertaken. As bisphosphonate treatment in post-menopausal women appeared to demonstrate a similar magnitude of benefit to that of other commonly used adjuvant strategies the debate assessed whether or not there was sufficient data to incorporate adjuvant bisphosphonates into standard practice and if so, in which patient populations.

1. Introduction

The Bone and Oncologist New Updates (BONUS) meeting is an annual conference, based in Canada that focuses on new advances in the multidisciplinary management of cancer related bone disease. An important goal of the meeting has been to drive research collaboration within the attending audience of basic scientists and clinicians, but also to produce guidelines and recommendations to the broader audience of health care workers involved in the care of cancer patients. The meeting has previous produced a number of documents covering basic science [1], translational research [2–4], clinical research [5–10] and practice guidelines [11,12]. Each year a debate is held on a controversial bone-related topic and so for the 2014 BONUS meeting, the debate focused on the recently presented meta-analysis by the Early Breast Cancer Trialists Collaborative Group (EBCTCG) on the use of adjuvant bisphosphonates in early stage breast cancer [13].

Given the recognized effects of bisphosphonates in metastatic breast cancer [14,15] and that potential anticancer effects have been demonstrated in preclinical [16], translational [17], patients with cancer therapy-induced bone loss [18] and population based-studies [19,20] a number of clinical trials assessing bisphosphonates' effect on outcome in early stage breast cancer have been performed. Many of these trials presented conflicting results [21,24], but a consistent trend of beneficial effect on breast cancer recurrence was seen in older women. Of concern was that a useful clinical effect might have been missed because of trial design, end-points used, and under-powering of clinical trials for sub-group analyses [16]. Hence, an individual patient data meta analysis was performed and presented at the San Antonio Breast Cancer Symposium, December 2013 [13]. As this was considered by the BONUS meeting organizers an important, but potentially controversial topic, a debate format was used to best demonstrate contrasting views. While the original title for the debate was "This house believes that adjuvant bisphosphonates represent a gold-standard for post-menopausal women with higher risk breast cancer" the debaters asked if they could amend the title. In this commentary, we summarize the debates findings, and incorporate comments from the audience.

2. All women with invasive breast cancer over 50 should be offered a bisphosphonate

2.1. Presenter – Dr. Alexander Paterson

Multiple trials have studied bisphosphonates as a component of adjuvant systemic therapy for breast cancer (Table 1). An initial

* Correspondence to: Division of Medical Oncology, The Ottawa Hospital Cancer Centre, 501 Smyth Road, Box 900, Ottawa, Ontario, Canada, K1H8L6.
Fax: +1 613 247 3528.
E-mail address: cjacobs@toh.on.ca (C. Jacobs).

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Table 1
Selected larger trials of adjuvant bisphosphonates in non-metastatic breast cancer.

Trial	Agent	*N*	Duration bone agent	Outcome measure	Outcome	95% CI	*p*	Summary
Powles (25)	Clodronate or placebo	1069	2 years	Relapse in bone (during treatment)	HR=0.44	0.22–0.86	0.018	Favors clodronate
				Relapse in bone (follow up)	HR=0.77	0.56–1.08	0.127	
				Mortality (all)	HR=0.77	0.59 1.0	0.047	Favors clodronate
				Mortality (Post menopausal subgroup)	HR=0.61	0.42–0.88		Favors clodronate
AZURE (23)	Zoledronic acid or standard care	3360	5 years	DFS (all)	HR=0.94	0.82–1.06		
				DFS (> 5 years post menopausal)	HR=0.77	0.69–0.96		Favors zoledronic acid
NSABP B-34 (22)	Clodronate or placebo	3311	3 years	DFS (all)	HR=0.91	0.78–1.07		
				BMFI (all)	HR=0.77	0.55–1.07	0.12	
				BMFI (> 50 years age at entry)	HR=0.62	0.4–0.95	0.022	Favors clodronate
				OS (all)	HR=0.84	0.67–1.05	0.13	
				OS (> 50 years age at entry)	HR=0.80	0.61–1.04	0.094	Favors clodronate
Meta-analysis (13)	Any bisphosphonate	22,982	Any duration	DR (all)	22.3 versus 20.9%		0.03	
				DR (post menopausal)	21.9 versus 18.4%		0.0003	Favors bone agent
				BC Mortality (all)	8.7 versus 16.9%		0.04	
				BC Mortality (post menopausal)	18.3 versus 15.2%		0.004	Favors bone agent

large trial of adjuvant clodronate conducted from 1989–1995 randomized 1069 patients with operable primary breast cancer to clodronate or placebo, given for two years. The primary endpoint of relapse in bone during the medication period showed a significant reduction in the occurrence of bone metastases in the clodronate arm, HR 0.44 (95% CI 0.22–0.86, $p=0.016$). However, for the entire period of follow up, the reduction in occurrence of bone metastases was non-significant (HR 0.77, 95% CI 0.56–1.08, $p=0.127$). The secondary endpoint of mortality also showed a significant reduction in the clodronate arm, HR 0.77 (95% CI 0.59–1.0, $p=0.047$) with an unplanned subgroup analysis of post-menopausal women showing a greater effect on mortality, with HR 0.61 (95% CI 0.42–0.88) [25].

More recently, the AZURE trial was a randomized open label trial of standard therapy versus standard therapy and zoledronic acid (given for five years) in 3360 women with stage II or III breast cancer. The primary endpoint of disease free survival (DFS) did not differ between the two groups (HR 0.94, 95% CI 0.82–1.06). However in a planned subgroup analysis, zoledronic acid improved DFS in women who were more than 5 years since menopause at trial entry [23]. A further similar trial, NSABP B34, randomized 3311 women with stage I–III breast cancer to oral clodronate or placebo for three years. Again DFS did not differ between groups at a median of 90.7 months follow up (HR 0.91, 95% CI 0.78–1.07) but in women greater than 50 years or older at study entry, clodronate showed benefits for recurrence free interval (HR 0.75, 95% CI 0.57–0.99, $p=0.045$), bone-metastases free interval (HR 0.62, 95% CI 0.40–0.95, $p=0.027$) and non-bone metastases free interval (HR 0.63, 95% CI 0.43–0.91, $p=0.014$). There was no benefit seen for overall survival between the two treatment arms although there was a numerical difference in deaths in women over 50 years of age, favoring the clodronate arm [22].

Given these and other conflicting results, an individual patient data meta-analysis was undertaken, with the results being presented at the San Antonio Breast Cancer Symposium, 2013 [13]. This analysis included 36 trials comprising 22982 patients, with primary outcomes of time to recurrence (TTR), time to first distant recurrence (TFDR) and breast cancer mortality. Planned subgroup analysis included menopausal status (if menopausal status was not documented, women >55 years of age were considered post-menopausal). Among all women the results showed no improvements in recurrence rate (26.5% no bisphosphonate versus 25.4% bisphosphonate, $p=0.08$), and a borderline improvement in distant recurrence rates (22.3% no bisphosphonate versus 20.9% bisphosphonate, $p=0.03$). Among the 11,036 post-menopausal women included in this analysis, significant improvements were seen in rates of distant recurrence (21.9% no bisphosphonate versus 18.4% bisphosphonate, $p<0.001$) and this difference was driven by a bisphosphonate-related reduction in bone recurrence (8.8% versus 5.9%, $p<0.001$). Ten-year breast cancer mortality was also significantly improved in post-menopausal women in the bisphosphonate arm with mortality rates of 18.3% in the no bisphosphonate group and 15.2% in the bisphosphonate group, $p=0.004$. This led the authors to conclude adjuvant bisphosphonates reduce bone metastases and improve survival in post-menopausal women, with a 34% reduction in risk of bone recurrence ($p<0.001$) and a 17% reduction in risk of breast cancer death ($p=0.004$). The effect was seen irrespective of bisphosphonate type. There were no effects in pre-menopausal women (in particular, no deleterious effects) and no effects on non-breast cancer deaths, contralateral breast cancer or local-regional recurrence.

In summary, this EBCCTG overview demonstrated a positive effect from bisphosphonates in a pre-determined sub-group analysis, resulting from consistent findings from multiple well-conducted trials. The finding is plausible, and the results support a modified vicious cycle hypothesis [26,27]. The exact mechanism of an enhanced anti-tumor effect of bisphosphonates in a low estrogen environment is uncertain, but certainly feasible [2,28,29]. One hypothesis may be that, by preventing enhanced bone destruction induced by the lack of estrogen, bisphosphonates interfere with the tumor-growth-supportive functions of bone-derived growth factors demonstrated in the vicious cycle hypothesis [26,28]. Alternately, low estrogen levels may not be the cause, other possibilities include increased levels of pro-inflammatory proteins leading to enhanced macrophage activity in the aging process reduced by bisphosphonates [30]. The magnitude of benefit of bisphosphonates is similar, if not greater than, other strategies that have been widely adopted in the breast cancer clinic. The absolute benefit in mortality for post menopausal women of 3.1% at 10 years compares to the estimated absolute benefit of