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Adjuvant bisphosphonates in early breast cancer: consensus guidance for clinical practice from a European Panel

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Bisphosphonates have been studied in randomised trials in early breast cancer to investigate their ability to prevent cancer treatment-induced bone loss (CTIBL) and reduce the risk of disease recurrence and metastasis. Treatment benefits have been reported but bisphosphonates do not currently have regulatory approval for either of these potential indications. This consensus paper provides a review of the evidence and offers guidance to breast cancer clinicians on the use of bisphosphonates in early breast cancer. Using the nominal group methodology for consensus, a systematic review of the literature was augmented by a workshop held in October 2014 for breast cancer and bone specialists to present and debate the available pre-clinical and clinical evidence for the use of adjuvant bisphosphonates. This was followed by a questionnaire to all members of the writing committee to identify areas of consensus. The panel recommended that bisphosphonates should be considered as part of routine clinical practice for the prevention of CTIBL in all patients with a *T* score of <−2.0 or ≥2 clinical risk factors for fracture. Compelling evidence from a meta-analysis of trial data of >18 000 patients supports clinically significant benefits of bisphosphonates on the development of bone metastases and breast cancer mortality in post-menopausal women or those receiving ovarian suppression therapy. Therefore, the panel recommends that bisphosphonates (either intravenous zoledronic acid or oral clodronate) are considered as part of the adjuvant breast cancer treatment in this population and the potential benefits and risks discussed with relevant patients.

Key words: adjuvant, bisphosphonates, breast cancer, guidelines

introduction

Bisphosphonates have regulatory approval and are part of standard care for the prevention and treatment of osteoporosis and the prevention of skeletal related events associated with bone metastases from metastatic solid tumours and multiple myeloma [1]. Bisphosphonates have also been studied in randomised trials in the adjuvant setting of early breast cancer to investigate their ability to prevent both cancer treatment-induced bone loss (CTIBL) and reduce disease recurrence and metastases. Bisphosphonates do not currently have regulatory approval for either of these indications. This consensus paper provides a

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review of the evidence and offers guidance on the use of bisphosphonates in both these additional settings.

aims

To provide guidance for the use of bisphosphonates in patients with early breast cancer, focusing on CTIBL and the prevention of metastases.

methods

consensus meeting

Using the nominal group methodology for consensus [2] individual leading experts from European stakeholders in the clinical management of breast cancer (medical/clinical oncologists, gynaecologists, surgeons), and experts in pre-clinical bone research were asked to present their opinions on the predefined aims of the consensus at a face-to-face meeting in October 2014. Following the presentations, a structured discussion was undertaken to collate individual expert opinions and review relevant published literature (identified as per 'Data sources' below).

consensus questionnaire

Following the consensus meeting, a series of questions were developed to consolidate expert opinions. Voting on each question was anonymous and in the format of 'agreement' or 'disagreement' (graded strong or slightly) or neutral if a panel member felt there was insufficient evidence or he/she had insufficient knowledge to support a recommendation. Questionnaires were completed by 24/26 (90%) of experts and data was assessed. Detailed voting records for each question addressed to the panel are available in supplementary Appendix S1, available at *Annals of Oncology* online.

data sources

A systematic literature search was conducted using Pubmed and Medline databases from 1970 to 2014. In addition, the Cochrane Register of Controlled Trials and databases of ongoing and unpublished trials http://www.clinicaltrials.gov were searched. Conference proceedings from San Antonio Breast Cancer Symposium, European Society of Medical Oncology and American Society of Clinical Oncology (2000–2014) were reviewed. The key studies are summarised in Figures 1 and 2. In addition, the panel had access to the EBCTCG meta-analysis findings before full publication.

cancer treatment-induced bone loss

The causes of bone loss in cancer patients and the functional consequences are multifactorial, occurring as a result of the anti-cancer therapies used to prevent tumour recurrence and pre-existing clinical risk factors for fracture (age, concurrent medications, i.e. glucocorticoids, smoking status, low body mass index, family or personal history of fragility fracture, *T* score <−2.5) [1, 3]. The speed of CTIBL depends on the menopausal status of the patients in addition to the cancer treatment received, and on average is more rapid than the natural rate of bone loss that occurs in post-menopausal women [1, 4].

pre-menopausal women

Pre-menopausal women have high circulating levels of ovarian secreted oestradiol and inhibins, which act directly on bone to maintain bone mass [5]. However, accelerated bone loss in pre-menopausal women will occur if ovarian failure is induced by anti-cancer treatment, or if the effects of oestrogen on bone are inhibited by selective oestrogen receptor modulators such as tamoxifen.

effects of chemotherapy. Chemotherapy probably does not have a clinically significant direct toxic effect on bone in women who maintain menses [6]. Early bone loss has been observed during chemotherapy, but this is likely due to the induction of menopause, high doses of glucocorticoids used as anti-emetics plus fatigue-related immobility, rather than the cytotoxic agents themselves [7].

effects of ovarian suppression. Loss or suppression of ovarian function from either chemotherapy or drugs affecting the hypothalamic–pituitary–gonadal axis such as GnRH/LHRH analogues has been shown to cause rapid bone loss that persists for the duration of amenorrhoea [8]. In patients who receive chemotherapy and remain permanently amenorrhoeic, the indirect effects of chemotherapy on bone loss continue after cessation of chemotherapy [9–11].

In patients receiving GnRH analogues to suppress ovarian function (OFS), accelerated bone loss occurs during treatment but there is recovery after treatment is stopped, especially in those patients who resume menses [12, 13]. In the largest trial of OFS with endocrine therapy in pre-menopausal women, bone mineral density (BMD) after 3 years was reduced by 11.3% and 7.3% at the lumbar spine and trochanter, respectively. Seventy-five percent of patients' regained menses after endocrine treatment stopped and BMD partially recovered (but did not reach baseline levels) at both skeletal sites over the next 2 years [14]. Moreover, bone loss in patients receiving anastrozole in addition to OFS was greater than that seen with tamoxifen plus OFS (−13.6% versus −9% at 3 years) [14]. The use of OFS and an aromatase inhibitor (AI) is likely to be increasing in routine clinical practice following a recent randomised trial showing significantly improved disease-free survival (DFS) in pre-menopausal women with high-risk disease treated with this endocrine strategy compared with the current standard, tamoxifen [15].

effects of tamoxifen. Tamoxifen is the most commonly used endocrine drug in pre-menopausal women with hormone receptor-positive breast cancer, acting as an anti-oestrogen in breast cancer cells but with effects in bone that are dependent upon prevailing oestrogen levels. In pre-menopausal women, where the bone microenvironment is rich in oestradiol, tamoxifen taken for 3 years resulted in bone loss [16]. The effects of prolonged durations of tamoxifen should be studied further, since pre-menopausal women with breast cancer may now be recommended to continue with adjuvant tamoxifen for up to 10 years [17].

post-menopausal women

There is no clear evidence for a direct effect of chemotherapy on bone loss in post-menopausal women. In addition, tamoxifen reduces fracture incidence compared with placebo in a low bone oestrogen environment [18] and thus does not contribute to

Trial population [ref]		Trial design	Outcomes
Diel *et al* [61]	*n* = 302 Stage I–III Premenopausal 36% Postmenopausal 64% ER+ve 75% ER–ve 25% DTC+ve bone marrow	Oral clodronate 1600 mg daily vs placebo for 2 years	Significant reduction in the incidence of bone metastases (*P* = 0.003) and improved survival (*P* = 0.001) for clodronate.
Powles *et al* [62]	*n* = 1069 Stage I–III Premenopausal 50% Postmenopausal 50% ER+ve 64% ER–ve 36%	Oral clodronate 1600 mg daily vs placebo for 2 years	Significantly reduced incidence of bone metastases (HR 0.692 *P* = 0.043) and improved OS (HR 0.768 *P* = 0.048) for clodronate. Nb. in a sub group analysis, postmenopausal woman had the greatest disease outcome benefit from clodronate
Saarto *et al* [63]	*n* = 299 Stage II–III premenopausal 48% postmenopausal 52% ER+ve 61% ER–ve 39%	Oral clodronate 1600 mg daily vs placebo for 3 years	Increase in extraosseaous metasases (45% vs 32%) in clodronate group with increased risk of death (46% vs 38%). In a sub group analysis postmenopausal woman with ER+ve disease did not gain a negative effect from clodronate.
Paterson *et al* [64] (NSABP-B-34)	*n* = 3323 Stage I–III Premenopausal % Postmenopausal % ER+ve 78% ER–ve 22%	Oral clodronate 1600 mg daily vs placebo for 3 years	No significant difference in DFS between groups. Post hoc analysis in woman >60 years shown a significantly improved bone (HR 0.64 95% CI 0.4–0.95 *P* = 0.047) and extraosseous (HR 0.63 95% CI 0.43–0.91 *P* = 0.014) metasasis free survival for clodronate.
Von Minckwitz *et al* (German GAIN study) [65]	*n* = 2015 Stage II–III Premenopausal 48% Postmenopausal 52% ER+ve 76% ER–ve 23%	Oral ibandronate 50 mg daily vs placebo for 2 years	No significant difference in DFS (HR 0.945 95% CI 0.768 –1.161 *P* = 0.589) or OS (HR1.04 95% CI 0.763–1.419) *P* = 0.803 between groups. DFS was non significantly longer in woman <40 and >60 years.
Kristensen *et al* [66]	*n* = 953 Stage I–II Premenopausal 67% Postmenopausal 33% ER+ve ~15% ER–ve ~60%	Oral pamidronate 150 mg twice daily vs placebo for 4 years	No significant difference in DFS (HR 1.03 95% CI 0.75–1.4 *P* = 0.86) or OS between groups.

Figure 1. Summary of major adjuvant trials evaluating oral bisphosphonates in early breast cancer.

endocrine therapy-related bone loss in this population. The major contributor to bone loss in a post-menopausal breast cancer population is the use of AIs.

bone effects of aromatase inhibitors. AIs improve disease outcomes in comparison to tamoxifen but are associated with increased fracture incidence [1]. These agents prevent the conversion of androgens to oestrogen by the aromatase enzyme, thereby rapidly and dramatically reducing circulating serum oestadiol levels [19]. This decline in oestradiol is associated with a 40% relative increase in fracture rate compared with tamoxifen [20]. When compared with placebo the excess fracture rate during AI therapy is less [21]. Reassuringly, the bone loss induced by AI therapy appears to partially recover after completion of treatment [22, 23].

management of cancer treatment-induced bone loss

Management of the bone loss associated with cancer therapies includes both lifestyle recommendations and pharmacological intervention [24–26]. All patients at risk of bone loss should be advised to take regular weight bearing exercise [27–29] and reduce smoking and alcohol consumption [3].

Pharmacological intervention for patients at risk of bone loss includes vitamin D supplementation (1000–2000 IU daily) as many breast cancer patients are not replete with vitamin D [30]. In addition, calcium supplementation (1000 mg daily) is recommended if dietary intake is inadequate. Anti-resorptive therapies have been proven to be effective in preventing CTIBL, although their efficacy is influenced by menopausal status and the rate of bone loss [1, 24–26].

Current fracture risk assessment tools are based on data from healthy post-menopausal women and do not adequately address the risks associated with treatments in younger pre-menopausal women. Guidelines from an UK expert panel [24] for pre-menopausal women with breast cancer have been published and discussed in a recent review by Hadji et al. [26]. Recommendations included informing patients of the risk of bone loss during cancer therapy and consideration of the use of bisphosphonates if the T score is <−2.0. However, how changes in BMD correlate to fracture risk needs further assessment since previous studies in pre-menopausal women have used changes in either BMD or biochemical markers of bone resorption as surrogates for fracture risk [29].

The evaluation of BMD and use of the WHO Fracture Risk Assessment Tool (FRAX) in post-menopausal women provides a reliable estimate of fracture risk. However, FRAX does not include anti-cancer treatments as a specific risk factor, and so may underestimate risk [3, 31]. Published guidelines recommend

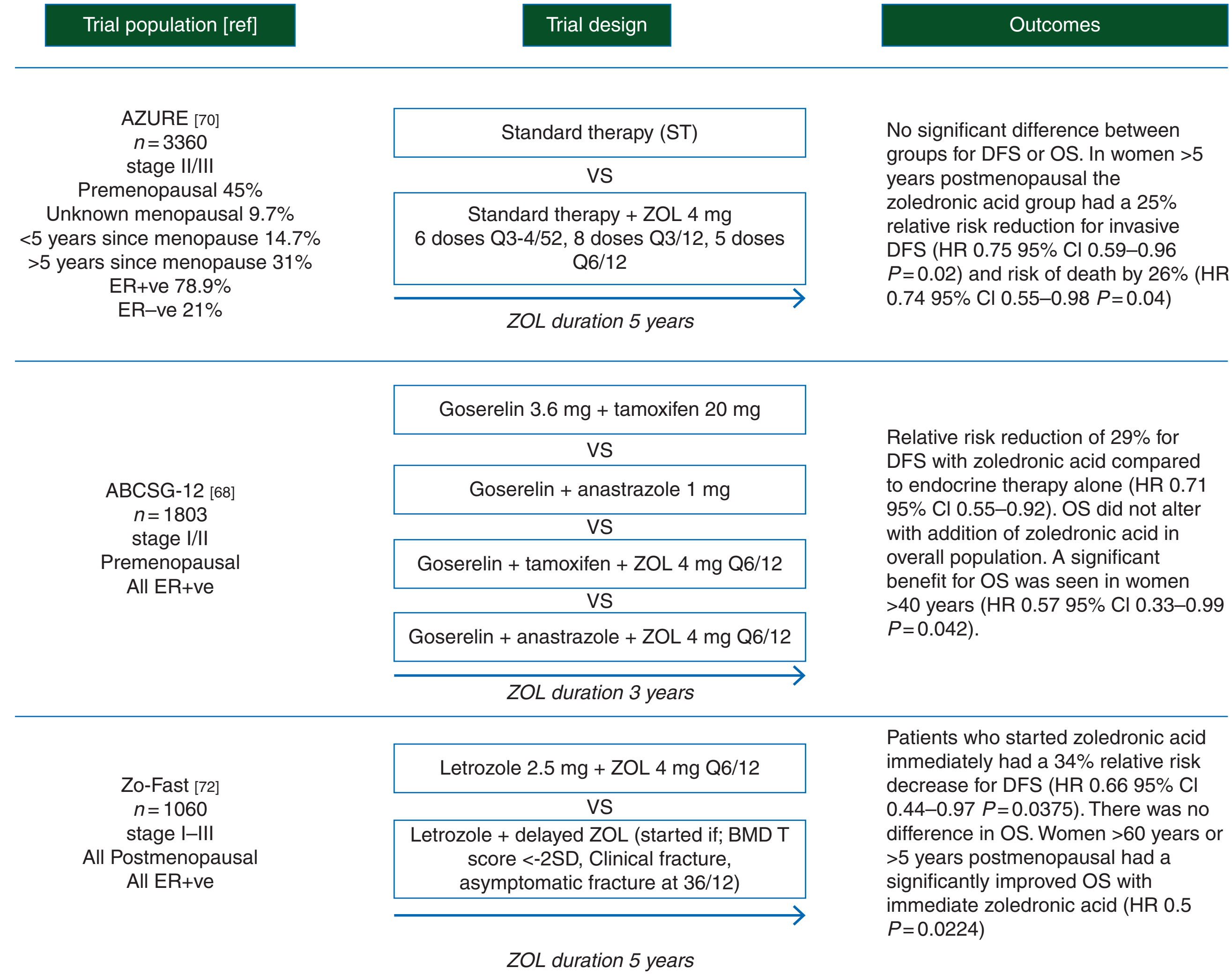


Figure 2. Summary of major adjuvant trials evaluating intravenous zoledronic acid in early breast cancer.

evaluation of BMD, fracture risk assessment and measurement of serum calcium, parathyroid hormone and 25-0H-vitamin D levels before and during AI therapy [24, 26, 32]. Anti-resorptive therapy is recommended in patients with a baseline *T* score of <−2.0 or two or more clinical risk factors for fracture [1, 24, 25].

In pre-menopausal women zoledronic acid, the most potent available bisphosphonate has been shown at a dose of 4 mg every 6 months to prevent the significant bone loss associated with goserelin + tamoxifen/anastrozole [14]. This schedule of zoledronic acid has also been shown to prevent bone loss associated with ovarian failure due to chemotherapy [9, 33, 34]. Other bisphosphonates have shown some ability to prevent the marked bone loss associated with ovarian suppression/failure but do not have a sustained effect on BMD in this population [10, 11, 35]. Zoledronic acid in addition to calcium and vitamin D supplementation is therefore recommended to combat the rapid bone loss in this clinical setting [1, 26].

In post-menopausal women, the choice of bisphosphonate is broader with evidence that ibandronate (150 mg oral monthly) [36], clodronate (1600 mg oral daily) [8], risedronate (35 mg oral weekly) [37], alendronate (70 mg oral weekly) [38] and zoledronic acid (4 mg i.v. 6 monthly) [39–41] all prevent the bone loss associated with use of AIs. Although these trials were not designed for a fracture-prevention end point, data from the osteoporosis setting have demonstrated a good correlation between BMD improvements and fracture prevention [1]. Recently, the more potent osteoclast inhibitor, denosumab, has been shown to halve the incidence and significantly extend the time to first clinical fracture in post-menopausal women receiving AIs, irrespective of baseline BMD [42].

toxicity and adherence

Although oral bisphosphonates are generally well tolerated, treatment adherence is reported to be poor, with up to 70% of patients discontinuing treatment in the first year [43]. Intravenous bisphosphonates avoid this issue but are associated with acute phase reactions and renal dysfunction [44] requiring renal monitoring and dose reductions for renal impairment. Osteonecrosis of the jaw (ONJ) is the most important adverse event associated with prolonged administration of potent inhibitors of bone resorption. ONJ is more common (incidence ∼1.3%) [45] when intravenous bisphosphonates are used monthly in the setting of advanced cancer but rare with less intensive use of intravenous

Table 1. Adjuvant bisphosphonate use to prevent osteoporosis and fracture

Areas of strong consensus (>80%)		
Should be considered in pre-menopausal women on ovarian suppression and an aromatase inhibitor		
Agree 23 (16 + 7; 96%);	Disagree 1 (0 + 1; 4%);	Neutral/abstain 0 (0%);
When used bisphosphonates should not be continued indefinitely		
Agree 20 (11 + 9; 83%);	Disagree 0 (0%);	Neutral/abstain 4 (17%);
Areas of modest consensus (60%–80%)[a]		
Treatment should be based on fracture risk algorithms ± BMD results		
Agree 17 (8 + 9; 71%);	Disagree 3 (2 + 1; 12%);	Neutral/abstain 4 (17%);
Should be considered in pre-menopausal women on ovarian suppression and tamoxifen		
Agree 17 (9 + 8; 71%);	Disagree 4 (0 + 4; 17%);	Neutral/abstain 3 (12%);
Zoledronic acid is the preferred agent for women receiving ovarian suppression		
Agree 17 (6 + 11; 71%);	Disagree 5 (1 + 1; 21%);	Neutral/abstain 2 (8%);
When used, bisphosphonates should be continued until the adjuvant treatment programme is complete		
Agree 17 (6 + 11; 71%);	Disagree 4 (1 + 3; 17%);	Neutral/abstain 3 (13%);
Bisphosphonates can be given in my health care system for this indication		
Agree 17 (6 + 11; 71%);	Disagree 3 (0 + 3; 12%);	Neutral/abstain 4 (17%);
Duration should depend on BMD results		
Agree 14 (4 + 10; 58%);	Disagree 5 (1 + 4; 21%);	Neutral/abstain 5 (21%);
Is not required in pre-menopausal women on tamoxifen alone		
Agree 15 (5 + 10; 62%);	Disagree 4 (2 + 2; 17%);	Neutral/abstain 5 (21%);
Areas of uncertainty or lack of consensus		
Treatment decisions should not be based on BMD results alone		
Agree 12 (3 + 9; 50%);	Disagree 9 (1 + 8; 37%);	Neutral/abstain 3 (12%);
Does not need to be considered in post-menopausal women on tamoxifen alone		
Agree 11 (1 + 10; 46%);	Disagree 8 (3 + 5; 33%);	Neutral/abstain 5 (21%);
Should be restricted to post-menopausal women receiving an AI		
Agree 12 (0 + 12; 50%);	Disagree 9 (7 + 2; 37%);	Neutral/abstain 3 (12%);
Any bisphosphonate can be used for post-menopausal women		
Agree 13 (3 + 10; 54%);	Disagree 9 (3 + 6; 37%);	Neutral/abstain 2 (8%);
Any bisphosphonate can be used for pre-menopausal women		
Agree 9 (0 + 9; 37%);	Disagree 9 (4 + 5; 37%);	Neutral/abstain 6 (24%);

[a]Number agreeing (strongly + slightly; %); number disagreeing (strongly + slightly; %).

bisphosphonates (6 monthly) or with oral bisphosphonates given for preservation of bone mass [46]. Nevertheless, before bisphosphonates are initiated, it is recommended that patients undergo a dental examination and maintain good oral hygiene while on treatment, avoiding invasive dental surgical procedures such as extractions or implant placement [1].

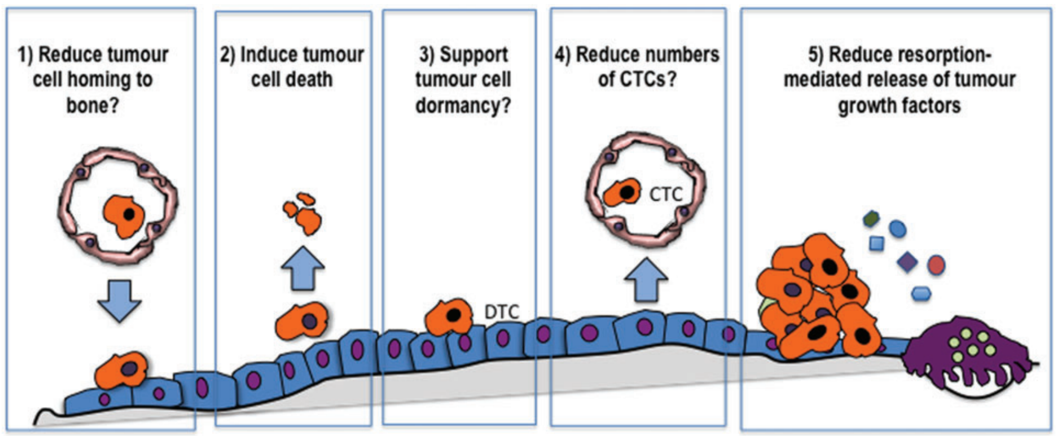
panel recommendations. The panel agreed that treatment decisions should take into account risk factors for fracture and measurement of BMD in all women receiving adjuvant therapy. Pre-menopausal women receiving OFS, especially when combined with an AI, were considered the highest priority for treatment and pharmacological intervention was least relevant for pre-menopausal women on tamoxifen alone. The panel recommended that treatment is continued until the adjuvant breast cancer treatment programme is complete, taking note of BMD results, but not continued indefinitely. Other than a preference for zoledronic acid in pre-menopausal women, there was variable preference on the choice of agent in post-menopausal women. Although there is not a specific license for bisphosphonate use in early breast cancer, the panel did not consider this a barrier to prescribing these agents (Table 1).

adjuvant use of bisphosphonates for prevention of metastases

pre-clinical and early phase clinical trial data

Pre-clinical studies using *in vivo* model systems have evaluated the anti-cancer properties of bisphosphonates at various stages of breast cancer progression (Figure 3) and demonstrated an ability to:

- 'prevent homing of tumour cells to bone' using zoledronic acid [47], ibandronate [48] and olpadronate [49] administered before tumour cell injection. In support of this, clinical studies have shown that both zoledronic acid [50–52] and ibandronate [53] decrease the number of DTCs in bone marrow aspirates from breast cancer patients;
- 'cause direct induction of tumour cell death in bone' when combined with chemotherapy *in vivo* [54];
- 'maintain dormancy of tumour cells in bone' with *in vivo* studies demonstrating that zoledronic acid [50] can prevent proliferation of dormant tumour cells in bone following increased bone turnover secondary to ovariectomy [55];
- 'inhibit release of growth factors from bone and interruption of the vicious cycle of bone metastasis' with *in vivo* data showing that bisphosphonates can slow tumour progression once bone



Other cell types in the bone/tumour microenvironment shown to be affected by BPs:

- **Osteoblasts:** Reduced by a single dose of Zol *in vivo* (79)
- **Macrophages:** Increased polarisation to M1 anti-tumour phenotype in mammary tumour, no evidence from bone metastasis models (80)
- **Immune cells:** Stimulation of immune cells by BPs affects tumour growth specifically in those tumours outside bone (81)

Figure 3. Potential effects of BPs in bone metastases.

metastases are formed [56–59], if used on a repeated schedule and especially in combination with chemotherapy [60].

These pre-clinical data showing an anti-tumour effect of bisphosphonates provided scientific rational for the subsequent randomised, controlled clinical trials.

adjuvant clinical trials of bisphosphonates to prevent metastases

Three randomised breast cancer trials initiated in the 1990s assessed the use of the oral bisphosphonate clodronate in addition to standard adjuvant therapy. The results were inconsistent with two trials reporting a reduction in bone recurrence and improved overall survival (OS) [61, 62], whereas the third suggested an adverse effect of clodronate with an increase in extra-osseous metastases [63] (Figure 1). Subsequent adjuvant trials were performed that recruited larger numbers of patients to receive oral bisphosphonates (NSABP-B34 with clodronate [64]; German GAIN study with ibandronate [65] and the Danish collaborative trial with pamidronate [66]) or the more potent intravenous bisphosphonate zoledronic acid (AZURE [67] and ABCSG-12 [68]; Figure 2). It was the results of these subsequent clinical trials that first identified a probable link between improved DFS outcomes with zoledronic acid in patients with low levels of female hormones at initiation of adjuvant therapy (discussed below). In addition, pre-clinical data supported the hypothesis that adjuvant bisphosphonates can prevent metastases and improve disease outcomes in the presence of low levels of both female and male hormones. An *in vivo* study evaluated the effects of zoledronic acid on the growth of DTCs in bone comparing ovariectomised (OVX) mice (modelling post-menopausal disease) and sham-operated mice (modelling pre-menopausal disease). The number of detectable tumours in bone was only reduced by zoledronic acid treatment in OVX animals, with no effect in sham-operated animals [55]. These data have been further supported by the same group using a prostate cancer model, with the ability of DTCs in bone to form detectable tumours inhibited by zoledronic acid only in castrated mice, not sham-operated [56]. The molecular mechanisms driving this differential effect of the drugs according to prevailing hormone levels remains an active area of research.

adjuvant clinical trials of bisphosphonates demonstrating the influence of menopausal status on DFS outcomes

The ABCSG-12 trial results were thought provoking. Although primarily a trial to evaluate different endocrine strategies including ovarian suppression with goserelin plus either tamoxifen or letrozole for good prognosis ER+ve pre-menopausal breast cancer, the 2×2 randomisation including 6 monthly zoledronic acid or control enabled evaluation of this bisphosphonate on disease outcomes. After 94.4 months median follow-up, relative risks of disease progression [hazard ratio (HR) = 0.77; 95% confidence interval (CI) 0.60–0.99; $P = 0.042$] and of death (HR = 0.66; 95% CI 0.43–1.02; $P = 0.064$) remain reduced by zoledronic acid [69].

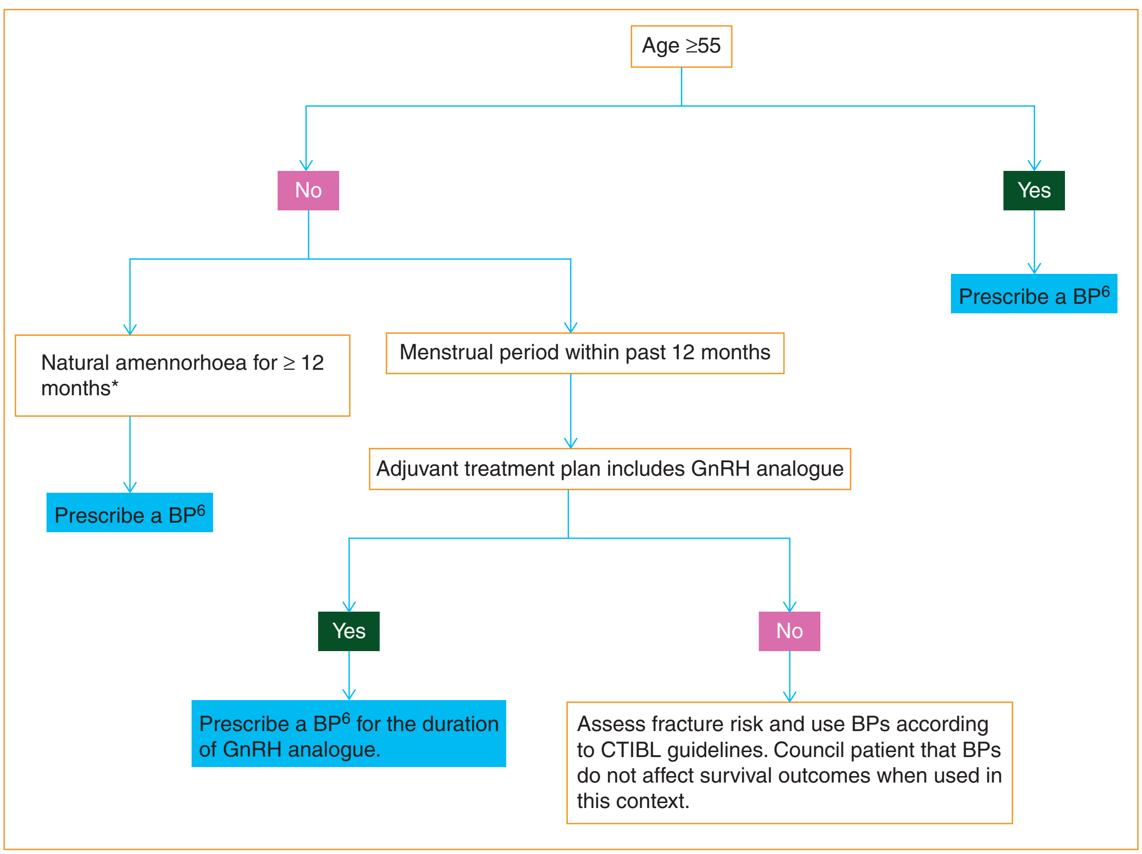
Shortly after publication of the initial findings from ABCSG-12 [68], the first results from the AZURE trial were announced. In this larger study, including both pre- and post-menopausal women with ER+ or ER− breast cancers, no improvements in either DFS or OS were seen [70]. However, women with established menopause at study entry (>5 years since last menses) did appear to benefit, leading to the hypothesis that the benefits of adjuvant bisphosphonates are (largely) restricted to women with low levels of reproductive hormones, achieved either through natural menopause or ovarian suppression therapy. The NSABP-B34 [64] and GAIN trials [65] also failed to demonstrate a significant benefit with bisphosphonates in the overall population. However, both studies suggested benefits of bisphosphonates in older patients (NSABP-B-34 over the age of 50; GAIN over the age of 60) providing further support to the hypothesis.

Several other trials evaluating zoledronic acid primarily as a bone protector during AI treatment of post-menopausal breast cancer also investigated the effects of bisphosphonate use on disease outcomes [40, 71, 72]. The largest of these (ZO-FAST) [71] reported fewer recurrences in women receiving immediate bone protection with zoledronic acid compared with the control arm where the bisphosphonate was only introduced months or years later if there were changes in BMD or a fracture that warranted intervention.

The improvement in disease outcomes in both the zoledronic acid and oral clodronate trials were predominantly and most consistently mediated by a reduction in bone metastases as the first distant metastatic site. The AZURE trial also reported different effects of zoledronic acid on extra-skeletal recurrence by menopausal status with benefit in post-menopausal women and an adverse impact on relapse outside bone in women who were pre-menopausal at study entry [67]. However, this heterogeneity of response outside bone has not been observed in other trials.

meta-analysis of adjuvant bisphosphonate trial data. Several selective, study level meta-analyses have been published suggesting a benefit in disease outcomes across adjuvant bisphosphonate trials with a variety of agents [41]. One of these specifically estimated the benefit in post-menopausal women and reported a significant improvement in DFS (HR = 0.82; 95% CI 0.74–0.92, $P \leq 0.001$) [73]. These data supported the notion that adjuvant bisphosphonates are likely to be most effective when there are low levels of female reproductive hormones due to natural/chemical menopause and helped trigger a more detailed meta-analysis.

To investigate the available evidence in a more robust and precise fashion, the Early Breast Cancer Trials Collaborative Group (EBCTCG) has conducted a formal individual patient data meta-analysis of data from 18 766 women involved in 26 randomised trials of adjuvant bisphosphonates for early breast cancer [74]. The majority of these patients received either oral clodronate 1600 mg daily or i.v. zoledronic acid 4 mg every 6 months or more frequent dosing as per the AZURE schedule [67]. 3453 and 2106 breast cancer recurrences and deaths were reported, respectively. For the entire population, bisphosphonates did reduce the number of patients with first distant recurrence in bone (RR = 0.83; 95% CI 0.73–0.94, $2P = 0.004$), but had less clear effects on time to any breast cancer recurrence (RR = 0.94; 95% CI 0.87–1.01, $2P = 0.08$), distant recurrence (RR = 0.92; 95% CI 0.85–0.99, $2P = 0.03$) or breast cancer mortality (RR = 0.91; 95% CI 0.83–0.99, $2P = 0.04$). However, in post-menopausal women ($n = 11\,767$), bisphosphonates not only improved recurrence in bone (RR = 0.72; 95% CI 0.60–0.86, $2P = 0.002$) but also overall breast cancer recurrence (RR = 0.86; 95% CI 0.78–0.94, $2P = 0.002$), distant recurrence at any site (RR = 0.82; 95% CI 0.73–0.92, $2P = 0.003$) and breast cancer mortality (RR = 0.82; 95% CI 0.73–0.93, $2P = 0.002$). Bisphosphonates did not appear to modify any disease outcomes in pre-menopausal women with a borderline significance test for heterogeneity by menopausal status ($2P = 0.06$). These results were maintained in a sensitivity analysis where the hypothesis generating trials (ABCSG-12 and



*If not clinically assessable i.e. hysterectomy/IUD then ensure serum FSH is in postmenopausal range. Ensure patient is not receiving concurrent therapies that can affect the HPG axis.

[6]Include vitamin D 1000-2000 IU and calcium 1000 mg daily.

Figure 4. Selection of patients suitable for adjuvant bisphosphonates to prevent metastases.

AZURE) were omitted; without these trials post-menopausal women continuing to show benefit across key recurrence and survival end points.

The risk reductions for relapse and mortality in post-menopausal women treated with bisphosphonates were similar irrespective of ER status or grade of the primary tumour, axillary lymph node involvement and use/non-use of chemotherapy, suggesting that menopausal status should be the main criterion for selection of patients for adjuvant bisphosphonates to prevent metastases.

The data also suggest that menopausal status at the initiation of adjuvant bisphosphonates is important. If this were not so, benefit would also be expected in women rendered post-menopausal by adjuvant chemotherapy. However, with the exception of women receiving ovarian suppression therapy at the start of adjuvant bisphosphonates, neither the AZURE data nor the meta-analysis could identify a subset of pre-menopausal women, for example those aged >45 years who have a very high likelihood of developing a chemotherapy induced menopause, who derived benefit from adjuvant bisphosphonates. This indicates the initial interaction between bisphosphonates and endocrine/paracrine factors in the bone microenvironment differentially influences the survival of tumour cells already disseminated into the bone/ bone marrow microenvironment at diagnosis (reviewed in Wilson et al. [75]).

patient selection, choice of agent, dose and duration of therapy. A clinical definition of 'post-menopausal' status, based on the widely accepted WHO definition (the permanent cessation of menstruation determined retrospectively after 12 months of amenorrhoea without any other pathological or physiological cause) [76], could be utilised in selecting patients for adjuvant bisphosphonates (see Figure 4). Biochemical classification of menopausal status based on serum FSH levels in the post-menopausal range before initiation of treatment may be of use in patients whose clinical status is unknown, e.g. due to hysterectomy or intrauterine devices. For those women who are not post-menopausal, bisphosphonates could be considered if treatment with GnRH/LHRH analogues is planned as part of adjuvant therapy, and continued for the duration of the ovarian suppression.

Table 2. Adjuvant bisphosphonates to prevent metastases in early breast cancer

Areas of strong consensus (>80%)		
Should be considered because the data are conclusive		
Agree 20 (17 + 3; 83%);	Disagree 2 (1 + 1; 8%);	Neutral/abstain 2 (8%);
Should be considered in post-menopausal women		
Agree 22 (14 + 8; 92%);	Disagree 1 (0 + 1; 4%);	Neutral/abstain 1 (4%);
Should not be considered in pre-menopausal women		
Agree 21 (17 + 4; 87%);	Disagree 1 (0 + 1; 4%);	Neutral/abstain 2 (8%);
Should be considered in pre-menopausal women receiving ovarian suppression therapy		
Agree 22 (11 + 11; 92%);	Disagree 1 (0 + 1; 4%);	Neutral/abstain 1 (4%);
Zoledronic acid or oral clodronate are the agents of choice		
Agree 21 (16 + 5; 87%);	Disagree 0 (0 + 0; 0%);	Neutral/abstain 3 (12%);
Areas of modest consensus (60–80%)[a]		
Should not be considered for all women with early breast cancer		
Agree 19 (14 + 5; 79%);	Disagree 3 (1 + 2; 12%);	Neutral/abstain 2 (8%);
Should be considered even though there is no regulatory approval for their use in this setting		
Agree 18 (15 + 3; 75%);	Disagree 3 (1 + 2; 12%);	Neutral/abstain 3 (12%);
When used, 6 monthly zoledronic acid is preferred to more intensive regimens		
Agree 17 (12 + 6; 75%);	Disagree 2 (1 + 1; 8%);	Neutral/abstain 4 (17%);
Can be given in my health care system as an off-label treatment based on a locally or nationally defined protocol or treatment guidance		
Agree 15 (8 + 7; 62%);	Disagree 6 (3 + 3; 25%);	Neutral/abstain 3 (12%);
Any bisphosphonate can be used		
Agree 3 (1 + 2; 12%);	Disagree 15 (5 + 10; 62%);	Neutral/abstain 6 (25%);
Should be considered in women with ER−ve early breast cancer		
Agree 15 (8 + 7; 62%);	Disagree 5 (2 + 3; 21%);	Neutral/abstain 4 (17%);
When used, bisphosphonate should be administered for 3–5 years		
Agree 15 (8 + 7; 62%);	Disagree 4 (1 + 3; 17%);	Neutral/abstain 5 (21%);
Areas of uncertainty of lack of consensus		
Should only be considered in post-menopausal women considered at intermediate or high risk of recurrence		
Agree 14 (7 + 7; 58%);	Disagree 7 (2 + 5; 29%);	Neutral/abstain 3 (12%);
Should only be considered in post-menopausal women with node-positive breast cancer		
Agree 7 (5 + 2; 29%);	Disagree 12 (5 + 5; 50%);	Neutral/abstain 5 (21%);
Weekly oral alendronate or risedronate should not be used		
Agree 12 (7 + 5; 50%);	Disagree 4 (0 + 4; 17%);	Neutral/abstain 8 (33%);
A patient on weekly oral alendronate or risedronate should be changed to zoledronic acid or clodronate		
Agree 13 (8 + 5; 54%);	Disagree 5 (0 + 5; 21%);	Neutral/abstain 6 (25%);

[a]Number agreeing (strongly + slightly; %); number disagreeing (strongly + slightly; %).

Prevention of CTIBL

Premenopausal women not receiving adjuvant ovarian suppression
- – Chemotherapy unlikely to have a direct affect on bone
- – Tamoxifen induces bone loss – long term effects need to be established
- – Assessment of fracture risk should include BMD assessment
- – Consider BPs if T score ≤2.0

Postmenopausal women at low risk of recurrence
- – Chemotherapy unlikely to have a direct affect on bone
- – Tamoxifen reduces fracture risk
- – AIs induce bone loss
- – Assessment of fracture risk should include FRAX assessment and BMD assessment
- – Ensure adequate calcium and vitamin D intake
- – Consider BPs if T score ≤2.0 or ≥2 clinic risk factors for fracture
- – BPs can include alendronate (70 mg PO weekly), risedronate (35 mg PO weekly), ibandronate (150 mg PO monthly), zoledronic acid (4 mg IV Q6 months), clodronate (1600 mg PO daily) (I,A)

Prevention of metastases and improving disease outcomes

Premenopausal women on adjuvant ovarian suppression
- – BPs should be considered to prevent CTIBL and metastases (I,A)
- – Recommended BP is zoledronic acid (4 mg IV Q6 months) or clodronate (1600 mg PO daily) (I,A)
- – BPs should be initiated at the start of adjuvant therapy (II,A)
- – Duration of BP treatment should not exceed duration of ovarian suppression unless indicated for low T score (3–5 years) (II,A)

Postmenopausal women at intermediate or high risk of recurrence
- – BPs should be considered to prevent metastases irrespective of fracture risk (I,A)
- – Recommended BPs are zoledronic acid (4 mg IV Q6 months) or clodronate (1600 mg PO daily) (I,A) alongside vitamin D supplementation and adequate calcium intake
- – BPs should be initiated at the start of adjuvant therapy (II,A)
- – Duration of BP treatment should be 3–5 years and only continued after 5 years if indicated by fracture risk (II,A)

Figure 5. Summary of key clinical points and levels of evidence for adjuvant BP treatment recommendations.

The meta-analysis was unable to demonstrate any important difference in disease outcome by type of bisphosphonate (amino versus non-amino), with the outcomes in the clodronate trials at least as good as those achieved with the more potent aminobisphosphonates. Additional data in support of this comes from the recently reported SWOG trial that showed no difference in DFS outcomes following 3 years of adjuvant clodronate, ibandronate and zoledronic acid [77]. The meta-analysis also found the intense treatment schedules of zoledronic acid, as used in AZURE, were of similar efficacy to the less intensive schedules of zoledronic acid 6 monthly or daily oral clodronate or ibandronate. There are no direct comparisons of duration of bisphosphonate treatment although the SUCCESS trial (NCT02181101) comparing 3 or 5 years of zoledronic acid treatment will help address this. In the meta-analysis, treatment benefits appeared early but there were insufficient data from trials of short-term (<2 years) adjuvant bisphosphonate use to recommend short durations of therapy with most of the data supporting treatment for 3–5 years.

Neither alendronate nor risedronate have been adequately evaluated in randomised adjuvant clinical trials. A retrospective review of over 20 000 women treated with osteoporosis doses of oral alendronate, risedronate or etidronate, either following a breast cancer diagnosis or started before and continued after diagnosis suggested that exposure to these agents reduced the risk of relapse and improved survival [78]. However, despite their established role in the prevention of osteoporosis, there are insufficient data to recommend their use for metastasis prevention.

panel recommendations. There was strong consensus that the data supported the use of adjuvant bisphosphonates in postmenopausal (whether natural or induced) women, with some experts (58%) suggesting further restriction to those considered at intermediate or high risk of recurrence rather than unselected use across all risk groups. There was consensus that a lack of regulatory approval for bisphosphonates in this setting should not preclude their use, with the majority indicating they could administer adjuvant bisphosphonates in their health care system as an off-label treatment based on a locally or nationally defined protocol or treatment guideline. The Panel was in agreement that either daily oral clodronate or i.v. zoledronic acid (Q6 monthly) are the preferred agents for metastasis prevention and recommended that the potential risks and benefits of adjuvant bone targeted treatment for 3–5 years alongside vitamin D supplementation and adequate calcium intake should be discussed with relevant patients (Table 2). With these regimens, the risk of ONJ is <1%.

summary of treatment recommendations

The overall consensus was that bisphosphonates should be used as part of routine clinical practice in the adjuvant management of CTIBL in 'at risk' patients and in the prevention of metastases in patients with low levels of female sex hormones (see Figure 5). Ongoing adjuvant trials of the osteoclast inhibitor denosumab (ABCSG 18 and D-CARE) will provide further information on the clinical role of mechanistically different adjuvant bone targeted treatments.

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disclosure

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Rituximab and risk of second primary malignancies in patients with non-Hodgkin lymphoma: a systematic review and meta-analysis

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Background: Addition of the anti-CD20 monoclonal antibody rituximab to chemotherapy improves response rates and survival in patients with B-cell non-Hodgkin lymphoma (NHL). However, rituximab induces a transient B-cell depletion and a dose-dependent T-cell inactivation that could impair T-cell immunosurveillance. The impact of rituximab on second primary malignancy (SPM) risk remains unclear so far. We thus carried out a systematic review to compare SPM risk among patients treated or not with rituximab.

Patients and methods: We retrieved trials from MEDLINE and EMBASE and updated data presented at American Society of Hematology and American Society of Clinical Oncology meetings from 1998 to 2013. We selected randomized, controlled trials addressing newly or relapsed/progressive B-cell NHL in which randomization arms differed only from rituximab administration. Two authors extracted data and assessed the study quality.

Results: We analyzed nine trials involving 4621 patients. At a median follow-up of 73 months, a total of 169 SPMs were observed in patients randomized to rituximab compared with 165 SPMs in patients not randomized to rituximab (OR = 0.88; 95% CI 0.66–1.19). The proportion of females, histology subtypes, use of rituximab in first line or in maintenance did not influence SPM risk ($P = 0.94$, $P = 0.80$, $P = 0.87$, $P = 0.87$, respectively). Cumulative exposure through prolonged administration in trials with rituximab maintenance did not contribute to an increased risk of SPM ($P = 0.86$).

Conclusion: Our meta-analysis suggests no SPM predisposition among NHL survivors exposed to rituximab at a median follow-up of 6 years.

Key words: meta-analysis, non-Hodgkin lymphoma, rituximab, second primary malignancies, secondary cancers, randomized controlled trials

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