Bisphosphonates for advanced breast cancer

a systematic review

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See Appendix A for more information.

Executive summary

Patients with advanced breast cancer commonly develop bone metastases. Cancer in bones can cause pain, fractures, hypercalcaemia and spinal cord compression, because cancer deposits can erode into bone using bone-absorbing cells. Bisphosphonates are drugs that reduce the activity of these bone-absorbing cells. Therefore, when breast cancer has spread to the bones, the use of bisphosphonates can reduce pain, fractures and other bone problems.[1] National Breast and Ovarian Cancer Centre (NBOCC) identified the need to review the evidence and update information about bisphosphonates for women with advanced breast cancer following consultation with a range of stakeholders and advisors.

A Cochrane review was first published in 2005,[1] with evidence updated until 2007, that assessed the effect of bisphosphonates on skeletal events (SE), bone pain, quality of life (QoL) and survival in women with early and advanced breast cancer. NBOCC conducted the current evidence review in April 2010 to identify evidence published since 2007 about the use of bisphosphonates for women with advanced breast cancer, building on the published Cochrane review as the primary reference for evidence prior to 2007.

Following a systematic review of the published literature, six full text citations for the review were identified including one meta-analysis, and five randomised controlled trials (RCTs). In addition to the peer-reviewed publications, eight guidelines were identified and a search of relevant conference proceedings identified three RCT abstracts of interest. Each trial identified in this review investigated different research questions and/or interventions, therefore comparisons between the trials or pooling of results was not possible. Various comparisons have been investigated including a head-to-head comparison of ibandronate to zoledronic acid and comparisons between zoledronic acid and denosumab, a new bone agent. Most studies were limited by relatively small numbers of patients and short treatment and follow-up times. A large trial has suggested that denosumab may result in improved skeletal outcomes compared to zoledronic acid in patients with breast cancer metastatic to bone.

The Cochrane review[1] remains the highest quality evidence available to support the use of bisphosphonates in addition to standard anti-cancer therapy in metastatic breast cancer with regards to reduction in risk of skeletal related events. A number of ongoing trials were identified which are anticipated to provide information regarding the optimal schedule of zoledronic acid and the relative benefits of oral ibandronate versus zoledronic acid.

1 Background

1.1 Breast cancer in Australia

Breast cancer is the most common cancer in women (excluding non-reportable skin cancer). In 2006, 12 614 invasive breast cancer cases (including both early and advanced breast cancer) were diagnosed, representing 28% of all reported cancer cases in Australian women. It is the second most common cause of cancer-related death for women after lung cancer.[2]

Advanced breast cancer includes both locally advanced and metastatic breast cancer. No national data is available on the prevalence of advanced breast cancer. The prevalence of advanced breast cancer is difficult to calculate as consideration needs to be given to cancers which are advanced at first diagnosis and to those early breast cancers that have progressed to advanced breast cancer.[3] National Breast and Ovarian Cancer Centre (NBOCC) is undertaking a statistical modelling study to estimate the prevalence of advanced breast cancer in Australia.

1.2 Clinical practice guidelines

The need to review the evidence and update information about bisphosphonates for women with advanced breast cancer was identified following consultation with a range of stakeholders and advisors.

NBOCC currently has two guideline recommendations about the use of bisphosphonates in advanced breast cancer in the *Clinical practice guidelines for the management of advanced breast cancer* published in 2001.[3] These recommendations state—

- *'When given regularly to women with advanced breast cancer and at least one bony metastasis, bisphosphonates enhance quality of life and reduce bone pain, the need for analgesics, the rate of development of new bony lesions, the incidence of hypercalcaemia and the need for radiotherapy to bony lesions'*.
- *'Bisphosphonates have a role in the treatment and prevention of bone pain in breast cancer'.*

1.3 Bisphosphonates for advanced breast cancer

Patients with advanced breast cancer commonly develop bone metastases. Cancer in bones can cause pain, fractures, hypercalcaemia and spinal cord compression, because cancer deposits can erode into bone using bone-absorbing cells. Bisphosphonates are drugs that reduce the activity of these bone-absorbing cells. Therefore, when breast cancer has spread to the bones, the use of bisphosphonates can reduce pain, fractures and other bone problems.[1]

There are two classes of bisphosphonates. The newer nitrogenous bisphosphonates are more potent than the non-nitrogenous bisphosphonates.

1. Nitrogenous (alendronate, ibandronate, neridronate, olapadronate, pamidronate, risedronate and zoledronic acid).

2. Non-nitrogenous (clodronate, etidronate and tiludronate).

A Cochrane review was first published in 2005, and was updated to include evidence until 2007, that assessed the effect of bisphosphonates on skeletal events (SE), bone pain, quality of life (QoL) and survival in women with early and advanced breast cancer.[1]

The purpose of this review was to identify evidence published since 2007 about the use of bisphosphonates for women with advanced breast cancer, building on the published Cochrane review as the primary reference for evidence prior to 2007.

2 Methods

The objective of the current review is to investigate the use of bisphosphonates in women with advanced breast cancer (ABC).

Research questions to be addressed in this systematic review were:

- What is the role of bisphosphonates in advanced breast cancer?
- What is the recommended scheduling (duration/dose/frequency of administration) for bisphosphonates use?
- What is the recommended mode of administration (IV vs. oral) of bisphosphonates?
- Are some bisphosphonate drugs more effective than others?

2.1 Inclusion criteria

2.1.1 Participants

Women with advanced breast cancer.

2.1.2 Intervention

Bisphosphonate treatment using nitrogenous or non-nitrogenous bisphosphonates.

Nitrogenous bisphosphonates include: alendronate, ibandronate, neridronate, olapadronate, pamidronate, risedronate and zoledronic acid.

Non-nitrogenous bisphosphonates include: clodronate, etidronate and tiludronate.

2.1.3 Comparison

Comparison groups of interest involve bisphosphonate compared with:

- no bisphosphonate or placebo
- different schedules, doses or administration routes of the same bisphosphonate
- another bisphosphonate or new generation bone acting agent.

2.1.4 Outcome measures

Outcome measures of interest were:

- the number, time to and/or type of skeletal related events (SREs) where SREs may include any or all of the following: new bone metastases, hospitalisation due to bone

pain, hypercalcaemia, fractures, the need for radiotherapy to treat bone metastases or the need for surgery, or spinal cord compression

- type of progression (bone metastases or other metastases)
- bone pain
- overall quality of life (QoL)
- adverse events (i.e. toxicities including osteonecrosis of the jaw (ONJ))
- bone health (bone mineral density)
- overall survival (OS).

2.2 Literature search

A systematic literature search was conducted in April 2010 to identify guidelines, systematic reviews and randomised controlled trials (RCTs) addressing the role of bisphosphonates in ABC, and in particular, the clinical outcomes listed above. The search was conducted using several databases (see Appendix B), including:

- Medline (OVID)
- Embase (OVID)
- Pubmed
- Cochrane library.

Additional papers identified from personal files and the reference lists of included papers were also sourced.

The search strategy, developed with input from a multidisciplinary working group (see Appendix A), used combined key terms which described ABC and bisphosphonates (see Appendix C). The search was limited to RCTs conducted in humans which were published from January 2007 to April 2010 in the English language.

After the removal of duplicate citations and the addition of further citations sourced, a total of 178 unique citations remained. The titles and abstracts of these citations were assessed by two reviewers independently to determine eligibility for the current review based on the criteria described above. Ineligible studies were determined using the exclusion criteria below. For citations which provided insufficient information to assess eligibility, the full text was retrieved for assessment by the same two reviewers.

In addition to the above databases, guideline and clinical trial websites were searched for relevant information. Specific international guideline organisations were searched as well as the National Guidelines Clearinghouse and the Guidelines International Network (GIN) guideline database. Further information on sites searched can be found in Appendix D.

The following conference websites were searched from January 2007 to May 2010 to identify recently presented abstracts on bisphosphonates for advanced breast cancer:

- American Society for Bone and Mineral Research (ASBMR) Annual Meeting
- American Society of Clinical Oncology (ASCO) Annual Meeting

- Annual San Antonio Breast Cancer Symposium
- Australia and New Zealand Bone and Mineral Society (ANZBMS) Annual Meeting
- European CanCer Organisation (ECCO) Conferences and Congresses.

2.2.1 Exclusion criteria

Individual study papers were excluded if they met any of the following criteria:

- not a randomised controlled trial
- not an original clinical study–publications not reporting the findings of original clinical studies including non-systematic reviews, editorials, opinion pieces and letters
- inappropriate population–studies conducted in a population other than patients treated for advanced breast cancer. Studies that were conducted in a general cancer population were included only if data on breast cancer patients were reported separately
- inappropriate intervention–studies not investigating bisphosphonates as defined in the inclusion criteria
- inappropriate outcomes–studies not reporting on any of the clinical outcomes as defined in the inclusion criteria
- not published in the English language
- published prior to 2007.

Based on these criteria, 130 articles were excluded. The full text of the remaining 48 citations were retrieved and assessed to identify which met the inclusion criteria for the review. After full text assessment five citations were identified as eligible for the current review (see Appendix E).

Full text citations for the review included one meta-analysis, one study comparing bisphosphonate schedules, one study comparing different bisphosphonates, one study comparing bisphosphonates with denosumab (a monoclonal antibody that binds to receptor activator of nuclear factor kappa-B ligand (RANKL), thereby inhibiting osteoclast function and bone resorption), and one subgroup analysis report from a RCT. An additional phase II RCT comparing IV ibandronate 15-minute infusion to 60-minute infusion was identified[4] however this study was not powered for a direct statistical comparison between the treatment arms, therefore was not included in this review. After completion of the systematic review, one randomised controlled trial published full results, previously included only in abstract form.[5] The full results have been incorporated into the relevant sections, bringing the number of full text citations to six.

In addition to the peer-reviewed publications, eight guidelines were identified and the conference search identified three abstracts of interest, including two for the randomised controlled trial recently published and included in this systematic review.

2.3 Data extraction

Data extraction was performed by one reviewer and verified by a second reviewer to ensure accuracy. Descriptive data extracted from the studies included characteristics such as population, interventions and primary outcomes. Outcome data extracted from the studies included OS, skeletal related events, adverse events and QoL.

3 Results

3.1 International guidelines

The following international guidelines were identified regarding the use of bisphosphonates to treat patients with advanced breast cancer and the main recommendations of the guidelines are summarised in Table 1. In addition, two publications were identified which provide international consensus statements regarding guidance on the use of bisphosphonates in solid tumours[6] and medical treatment of metastatic breast cancer, including bisphosphonate therapy.[7]

Table 1. International guidelines for bisphosphonates and advanced breast cancer

Guideline	Recommendation
ASCO (2003)[8] ***Update on the Role of Bisphosphonates and Bone Health Issues in Women With Breast Cancer***	• For patients with plain radiographic evidence of bone destruction, intravenous pamidronate 90mg delivered over 2 hours or zoledronic acid 4mg over 15 minutes every 3 to 4 weeks is recommended. • There is insufficient evidence supporting the efficacy of one bisphosphonate over the other. • Starting bisphosphonates in women who demonstrate bone destruction through imaging but who have normal plain radiographs is considered reasonable treatment. • Starting bisphosphonates in women with only an abnormal bone scan but without evidence of bone destruction is not recommended. • The presence or absence of bone pain should not be a factor in initiating bisphosphonates. • In patients with a serum creatinine less than 3.0mg/dL (265µmol/L), no change in dosage, infusion time, or interval is required. Infusion times less than 2 hours with pamidronate or less than 15 minutes with zoledronic acid should be avoided. Creatinine should be monitored before each dose of either agent in accordance with US Food and Drug Administration (FDA) labelling. • Oncology professionals, especially medical oncologists, need to take an expanded role in the routine and regular assessment of the osteoporosis risk in women with breast cancer. The panel recommends an algorithm for patient management to maintain bone health.
Cancer Care Ontario (2004)[9] ***Use of Bisphosphonates in Women with Breast Cancer***	• Women with breast cancer who have bone metastases should be offered treatment with oral clodronate, intravenous pamidronate, or intravenous zoledronate. • In patients with bone metastases and pain, treatment with pamidronate, zoledronate, or clodronate may be a useful adjunct to conventional measures for pain control. • Bisphosphonates are not recommended to prevent bone metastases or improve survival in women with locally advanced breast cancer or non-skeletal metastases. • There is no evidence from clinical trials that address the optimal duration of bisphosphonate use.

Guideline	Recommendation
	• There are no data on the efficacy of bisphosphonates in men with breast cancer, however, it is reasonable to recommend the use of bisphosphonates in men with breast cancer that is metastatic to bone.
ESMO (2009) [10] ***Locally recurrent or metastatic breast cancer***	• Bisphosphonates should be used for the treatment of hypercalcaemia, to palliate symptoms and decrease risk of bone events from clinically evident bone metastases. • The timing and optimal duration of bisphosphonates are unknown.
NCCN (2009)[11] ***Clinical Practice Guidelines in Oncology – Breast Cancer***	• Women with bone metastasis, especially if lytic, should be given a bisphosphonate in combination with calcium citrate and vitamin D if expected survival is 3 months or longer and creatinine levels are below 3.0mg/dL. • Bisphosphonates are given in addition to chemotherapy or endocrine therapy. • The use of a bisphosphonate is generally the preferred intervention to improve or maintain bone mineral density for women with breast cancer and osteopenia or osteoporosis. • Current clinical trials support the use of bisphosphonates for up to 2 years. Longer durations of bisphosphonate therapy may provide additional benefit, but this has not yet been tested in clinical trials. • Women treated with a bisphosphonate should undergo a dental examination with preventive dentistry prior to the initiation of therapy.
NICE (2009)[12] ***Advanced breast cancer: diagnosis and treatment***	• Consider offering bisphosphonates to patients newly diagnosed with bone metastases to prevent skeletal-related events and reduce pain. • The choice of bisphosphonate for patients with bone metastases should be a local decision, taking into account patient preference and limited to preparations licensed for this indication.
SIGN (2005)[13] ***Management of breast cancer in women***	• Bisphosphonates should be routinely used in combination with other systemic therapy in patients with metastatic breast cancer with symptomatic bone metastases. The choice of agent for an individual patient depends on individual circumstances.

ASCO=American Society of Clinical Oncology; ESMO=European Society for Medical Oncology; NCCN=National Comprehensive Cancer Network; NICE=National Institute for Health and Clinical Excellence; SIGN=Scottish Intercollegiate Guideline Network

Recommendations of an international expert panel regarding use of bisphosphonates in solid tumours (2008)[6]

The summaries of relevant recommendations from an international interdisciplinary expert panel are:

- In breast cancer, a nitrogen-containing bisphosphonate (N-BP) is preferably offered to patients with metastatic bone disease (MBD). Generally, IV administration is preferable; however, oral administration should be considered for patients who cannot or do not have to attend regular hospital care.
- Bisphosphonate (BP) therapy is a major factor contributing to control of pain due to MBD.

- Patients at risk of developing chemotherapy or hormone deprivation therapy-induced or hormone deprivation therapy-induced osteopenia or osteoporosis should be considered for preventative BP therapy. Presently the strongest evidence is on favour of zoledronic acid.
- Dosing regimens of BP therapy should follow the scientific data and respective regulatory recommendations and adjustments due to pre-existing medical conditions.
- Since the risk of SREs is continuous, the expert panel recommends continuing treatment until 2 years, even if a patient experiences a bone event. Continuation of therapy beyond 2 years based on an individual risk assessment is recommended.
- Transient acute-phase reactions are no reason for treatment discontinuation and can be managed with preventative or therapeutic analgesics (e.g. paracetamol or ibuprofen).
- In patients with renal impairment receiving IV BP, lower doses, longer infusion times, and selecting a BP with best possible renal tolerability (e.g. ibandronate) is recommended.
- To avoid renal toxicity with IV BP, patients should be adequately hydrated before treatment, and appropriate monitoring of serum creatinine is recommended.
- Calcium and vitamin D3 should be considered from the start of therapy with BP.
- In case of oral administration, patients need to be instructed to comply well with the dosage prescriptions to prevent gastrointestinal problems and maintain the adherence to therapy.
- Before starting N-BP treatment, patients should have a dental examination and appropriate treatment and should be advised to maintain good oral hygiene.
- For each patient with ONJ, an individual benefit/risk evaluation should be carried out to assess continuation or temporary discontinuation of BP therapy.

Central European Cooperative Oncology Group (CECOG) (2009)

The third consensus on medical treatment of metastatic breast cancer[7] by CECOG includes recommendations on bisphosphonate therapy for bone metastases:

- The strongest evidence for efficacy in prevention of skeletal morbidity in patients with breast cancer and bone metastases is available for IV bisphosphonate preparations, but no trial has directly compared oral with IV preparations. Evidence from randomised clinical trials in patients with breast cancer and bone metastases indicates that the use of bisphosphonates can reduce and delay the incidence of skeletal morbidity.
- Evidence supports the use of bisphosphonates with or without other anticancer treatment.
- Although most trials evaluated bisphosphonate treatment administered for a maximum of 2 years, the optimal duration of this treatment is unknown. The American Society of Clinical Oncology guidelines on the use of bisphosphonates in women with breast cancer recommend that bisphosphonate therapy should be continued until there is a substantial decline in patient performance status.
- Currently, there are insufficient data on the use of bisphosphonates in women without metastatic bone involvement or without hypercalcaemia of malignancy.

3.2 Systematic reviews

A meta-analysis was published in 2007 which evaluated the effect of oral clodronate for breast cancer, on overall survival, bone metastases-free survival and non-skeletal metastases-free survival,[14] including four RCTs for patients with advanced breast cancer. While the meta-analysis was published after the Cochrane review, all of the trials included in the meta-analysis were published prior to 2005 therefore were also included in the Cochrane review.[1] The meta-analysis found no statistically significant difference in overall survival (HR 0.71, 95% CI 0.40–1.26), bone metastasis-free survival (HR 0.68, 95% CI 0.34–1.36) or non-skeletal metastasis-free survival (HR 0.95, 95% CI 0.31–2.91) in advanced breast cancer patients receiving clodronate compared to placebo or no treatment.

3.3 Included studies

3.3.1 Description of studies

Five full text papers describing randomised controlled trials were identified. All papers investigated patients with advanced breast cancer with bone metastases. Each paper investigated different interventions, therefore results are presented for each study separately. The primary outcomes of most trials focused on bone turnover markers which were not specified outcomes of this systematic review, however the trials also reported on skeletal related events and/or adverse events, therefore are included. Most trials are reported over a short follow-up period (around three months) therefore data on overall survival and disease progression are limited.

One trial investigated different schedules of the same bisphosphonate. Generali *et al* (2008)[15] randomised 44 women to either administration of IV zoledronic acid in the morning (11.00am) or to administration at night (11.00pm).

One international phase III trial was identified which compared oral ibandronate (n=137) to IV zoledronic acid (n=138).[16]

One phase II trial was identified which compared open label IV bisphosphonate (n=43) to subcutaneous injection of various doses of denosumab (n=211).[17] A phase III trial compared patients randomised to subcutaneous denosumab (n=1026) with those randomised to IV zoledronic acid (n=1020) and the primary end-point was time to first on-study SRE.[5]

One paper reported on a subset analysis from an RCT which compared zoledronic acid with pamidronate for breast cancer patients with bone metastases. The subset analysis was conducted in patients who were treated with zoledronic acid, and compared patients who had normal or elevated urinary N-telopeptide of type I collagen (NTX) levels at baseline.[18]

In addition, three abstracts were identified from conference proceedings. One abstract provided results on patient preferences from a randomised study of oral ibandronate and oral clodronate.[19] Two earlier abstracts were identified from the large phase III trial investigating denosumab compared to zoledronic acid which have been superseded by the full text publication.[5,20-21]

Table 2. Study characteristics of included studies

Title	Location	Intervention	Comparison	Participants	Outcomes
Different schedules of same bisphosphonate					
Generali 2008[15] Phase III RCT	Italy	IV zoledronic acid (4mg, 15min infusion) in the morning at 1100 hours, every 4 weeks for 4 months (n=22)	IV zoledronic acid (4mg, 15min infusion) at night at 2300 hours, every 4 weeks for 4 months (n=22)	Breast cancer patients with bone metastases	Bone turnover markers; bone pain
Comparison of different bisphosphonates					
Body 2007[16] Phase III RCT	International	Oral ibandronate 50mg daily for up to 12 weeks Safety analysis n=137 ITT analysis n=128	IV zoledronic acid 4 mg every 4 weeks 15-minute infusion for up to 12 weeks Safety analysis n=137 ITT analysis n=126	Female patients with histologically confirmed breast cancer and at least one osteolytic or mixed bone lesion confirmed by radiological assessment.	Markers of bone turnover; adverse events; bone pain
Jagdev 2007[19] RCT Abstract		Oral ibandronate for 2 months followed by oral clodronate for 2 months (n=23)	Oral clodronate for 2 months followed by oral ibandronate for 2 months (n=23)	Women with breast cancer bone metastases	Patient preferences; pain; symptoms
Bisphosphonate vs. denosumab					
Lipton 2008[17] Phase II RCT	International	Open-label IV bisphosphonate (zoledronic acid, pamidronate or ibandronate) every 4 weeks through 21 weeks (n=43)	5 blinded cohorts of SC injections of denosumab of varying dose and/or schedule every 12wks through 21 weeks. Results are reported here for combined denosumab arms (total n=211)	Patients who had breast cancer with radiologic evidence of bone metastases	Bone turnover markers; SREs (fracture, surgery or radiation to bone, or spinal cord compression); safety
Stopeck 2010[5] Phase III RCT	International	IV zoledronic acid 4mg every 4 weeks (n=1020)	SC denosumab 120mg every 4 weeks (n=1026)	Breast cancer patients with radiographic evidence of at least one bone metastasis	SREs; adverse events; survival
Subgroup analysis					
Lipton 2007[18] Subgroup analysis of RCT	USA & Canada	IV zoledronic acid with normal NTX levels at baseline	IV zoledronic acid with elevated NTX levels at baseline	Breast cancer patients with bone metastases	SREs; time to progression of disease in the skeleton; survival

ITT=intention to treat; IV=intravenous; NTX= N-telopeptide of type I collagen; RCT=randomised controlled trial; SC=subcutaneous; SRE=skeletal related event; ZA=zoledronic acid

3.3.2 Results

The studies identified are listed and described below under the research questions to be addressed by this review.

What is the role of bisphosphonates in advanced breast cancer?

Studies evaluating bisphosphonates compared to placebo/no treatment

Since the Cochrane review update in 2007, no additional trials were identified which compared the use of bisphosphonates in ABC to placebo or no additional treatment.

What is the recommended scheduling (duration/dose/frequency of administration) for bisphosphonates use?

Studies comparing different schedules of bisphosphonates

IV zoledronic acid morning vs. IV zoledronic acid night

Generali *et al* (2008)[15] compared administration of IV zoledronic acid in the morning (11.00am) to administration at night (11.00pm). Twenty-two women were randomised to each arm, the primary outcome of this study was bone turnover markers. Blood samples were collected at defined intervals up to 84 days. In addition, bone pain was evaluated with a validated pain questionnaire at baseline and before each drug administration, after 28, 56 and 84 days.

Adverse events

Twenty patients (45.4%), 10 in each arm, experienced acute-phase reactions lasting no more than a few days after ZA administration.[15]

Bone health

Similar percentage changes of bone turnover marker levels were seen whether zoledronic acid was administered in the morning or at night, with decreasing levels observed for NTX, cross-linked C-terminal telopeptide of type I collagen (CTX), alkaline phosphatise (ALP) and osteocalcin. Parathyroid hormone significantly increased in both arms however was lower in the night arm.[15]

Bone pain

Bone pain was evaluated at baseline and before each treatment using a validated pain questionnaire which included items on performance status, analgesic consumption and mobility, with a resulting pain score of 0−19. The study reported that administration of zoledronic acid led to a decrease in bone pain without any difference between treatment arms, however specific details were not provided.[15]

What is the recommended mode of administration (IV vs. oral) of bisphosphonates?

Studies comparing modes of administration of the same bisphosphonate

No trials were identified which compared the same bisphosphonate using different modes of administration (such as oral compared to IV). One international phase III trial compared oral to IV bisphosphonates, however a different bisphosphonate was administered in each arm.[16] Results from this study are reported in the section titled *Studies comparing different bisphosphonates*.

Are some bisphosphonate drugs more effective than others?

Studies comparing different bisphosphonates and/or mode of administration

Oral ibandronate vs. IV zoledronic acid

One international phase III trial was identified which compared oral ibandronate (n=137) to IV zoledronic acid (n=138).[16] The primary outcome of this 12 week trial was the assessment of bone turnover markers, however bone pain and adverse events were also reported.

Overall survival

Two deaths were reported in the ibandronate arm, both due to disease progression. One death was reported in the zoledronic acid due to cerebral haemorrhage considered related to the underlying malignant disease.[16]

Adverse events

Adverse events were recorded to assess safety and tolerability (see Table 3). Patients given ibandronate described fewer adverse events overall (65%) compared with zoledronic acid (76%), particularly in the first three days of treatment (8% vs. 48% respectively). The incidence of adverse events considered by the investigator as being treatment-related was 22% in the ibandronate arm and 51% in the zoledronic acid arm.[16]

Table 3. Adverse events reported in Body 2007[16]

Adverse event	Oral ibandronate	IV zoledronic acid
	%	%
Any adverse event	65	75.9
Adverse events considered treatment related by the investigator	21.9	51.1
Adverse events during the first 3 days of the study	8	47.5
Serious adverse events	5.8	8
Pyrexia	0	16.8
Influenza-like symptoms	0.7	5.1
Treatment-related musculoskeletal and connective tissue disorders	11	20.4
Bone pain	5.8	12.4
Nervous system disorders	2.2	11
Musculoskeletal and connective tissue disorders	10.95	20.44

Adverse event	Oral ibandronate	IV zoledronic acid
	%	%
Gastrointestinal disorders	10.95	8.03
General disorders and administration site conditions	3.65	32.85
Nervous system disorders	2.19	10.95

IV=intravenous

Bone health

Bone turnover markers (Serum and urinary CTX, Bone ALP, PINP, OC) were significantly reduced with either bisphosphonate. The reductions in CTX (serum and urinary) were statistically equivalent for ibandronate and zoledronic acid.[16]

Bone pain

Bone pain was evaluated every 4 weeks using a 5-point scoring system. In addition analgesic consumption and radiotherapy used to treat bone pain was recorded. The mean changes in bone pain during the last week or the last 48 hours of the study were not significantly different between the treatment arms. The change in mean analgesic consumption at week 12 compared with baseline was also not significantly different between the treatment arms. While more patients on ibandronate received radiotherapy for treatment of bone pain than in the zoledronic acid arm, the difference was not statistically significant (18 patients versus 9 patients, respectively, p=0.07). The majority of patients receiving radiotherapy for bone pain were from one site in Russia. The study authors note that differences between patients receiving radiotherapy and analgesia are likely to be due to different clinical practice between centres.[16]

Rates of bone pain were also reported with other adverse events (see Table 3). Patients on ibandronate appeared to report lower rates of bone pain (6%) compared to those on zoledronic acid (12%) (statistical significance was not reported).[16]

Other outcomes reported

There was no evidence of deterioration in renal function in either treatment group.[16]

Oral ibandronate vs. oral clodronate

An abstract was presented at the ASCO meeting in 2007 which examined patient preferences between oral ibandronate and oral clodronate.[19] Forty-six women were randomised to receive one drug for two months, then crossed-over to receive the second drug for two months i.e. 23 patients received ibandronate followed by clodronate and 23 patients received clodronate followed by ibandronate. Patients reported pain and symptoms at baseline, at cross-over and at the end of the study. Patient preferences were assessed at the end of the study.

Patient preferences

Forty-one patients were available for patient preference assessment as five patients discontinued the study. One patient did not state a preference, 26 preferred ibandronate (63%) and 14 preferred clodronate (35%). Reasons for preference for ibandronate include tablet size (p=0.001) and number of tablets (p<0.001).[19]

Adverse events

Patients on ibandronate reported higher rates of toxicity than clodronate for nausea (17% vs. 9.7%), indigestion (9.7%, 4.8%) and pain flare (7.3%, 4.8%). Whether or not these differences were statistically significant was not reported in the abstract.[19]

Newer drugs to treat breast cancer patients with bone metastases

One phase II trial was identified which randomised patients to receive open label IV bisphosphonate (zoledronic acid, pamidronate or ibandronate) (n=43) or one of five denosumab treatment groups of various doses (n=211; 42 or 43 patients in each denosumab arm) for 21 weeks, with follow-up up to 57 weeks.[17] For the purposes of this review to compare bisphosphonates to denosumab, the results for the combined denosumab arms are reported.

The same authors published a full text paper in 2010[5] from a large phase III trial comparing zoledronic acid (n=1020) and denosumab (n=1026), with results at 34 months from first patient enrolment.

Both trials compared subcutaneous injections of denosumab with IV bisphosphonate.

Overall survival

By week 57 in the phase II trial, there were eight deaths in the bisphosphonate arm (19%) and 32 deaths in the denosumab arms (15%).[17]

In the phase III trial, overall survival was equivalent between denosumab and zoledronic acid groups (HR 0.95, 95% CI 0.81−1.11, p=0.49).[5] While actual rates were not reported, overall survival at 2 years is estimated from figures provided in the paper to be approximately 65% in both groups.

Time to progression

In the phase III trial, disease progression was equivalent between denosumab and zoledronic acid groups (HR 1.00, 95% CI 0.89−1.11, p=0.93).[5] While actual rates were not reported, overall disease progression at 2 years is estimated from figures provided in the paper to be approximately 25% in both groups.

Adverse events

Ninety-five percent of patients in both arms reported an adverse event by week 57 in the phase II trial.[17] No cases of osteonecrosis of the jaw were reported in either arm. Adverse events reported are presented in Table 4.

Table 4. Adverse events reported in Lipton 2008[17]

Adverse event (AE)	IV Bisphosphonate		All Denosumab	
	n	%	n	%
No of patients reporting serious AEs	15	35	75	36
Number of patients reporting any AEs	41	95	200	95
Treatment-related AEs	13	30	45	21
Serious Treatment related AEs	0	0	0	0
Withdrawals from the study because of AEs	1	2	5	2
AEs reported by >10% of patients				
Nausea	10	23	47	22
Vomiting	8	19	36	17
Diarrhoea	7	16	35	17
Asthenia	12	28	34	16
Back pain	4	9	30	14
Fatigue	5	12	28	13
Headache	8	19	28	13
Bone pain	8	19	26	12
Constipation	7	16	26	12
Arthralgia	13	30	24	11
Anaemia	2	5	23	11
Pain in extremity	8	19	21	10
Cough	7	16	18	8
Pyrexia	9	21	18	8
Oedema, peripheral	6	14	14	7
Dyspnoea	5	12	12	6

In the phase III trial, rates of overall, severe and serious adverse events were similar between zoledronic acid and denosumab groups (Table 5).[5] The authors of this trial considered these adverse events to be mostly reflective of toxicities related to concomitant therapies or complications of underlying cancer. Of the 20 adverse events identified with nominal between-group p value<0.05 (unadjusted for multiple comparisons), 18 were more common with zoledronic acid, including pyrexia, bone pain, arthralgia, renal failure and hypercalcaemia, and two were more common with denosumab, namely toothache and hypocalcaemia. Acute-phase reactions occurring within the first 3 days after treatment were more common with zoledronic acid (27%) than with denosumab (10%). Adverse events potentially associated with renal toxicity occurred more frequently with zoledronic acid than denosumab (9% vs. 5% respectively, p=0.001).

Osteonecrosis of the jaw (ONJ) occurred in 20 patients on denosumab (2%) and 14 patients on zoledronic acid (1.4%) (p=0.39).[5] At the reporting date, approximately 50% of ONJ cases had resolved in each treatment group. The study authors noted that ONJ occurred as early as 6 months after randomisation. The majority of patients who developed ONJ had known risk factors for ONJ, including history of dental extraction, poor oral hygiene, or use of dental appliance (90% in the denosumab group and 71% in the zoledronic acid group). Seventy-five per cent to 79% of patients who developed ONJ were receiving or had received chemotherapy. While toothache was more common with denosumab, this was not associated with the development of ONJ.

Table 5. Adverse events reported in Stopeck 2010[5]

Adverse event (AE)	Zoledronic acid	Denosumab
Rates of AEs	97%	96%
Grade ≥ 3 AEs	63%	60%
Serious AEs	46%	44%
Infectious AEs	49%	46%
Infectious serious AEs	8%	7%
AEs potentially associated with renal toxicity	9%	5%
AEs leading to treatment discontinuation	12%	10%
New primary malignancy	0.5%	0.5%
AEs reported by ≥20% of patients		
Nausea	38%	35%
Fatigue	32%	30%
Arthralgia*	29%	25%
Back pain	26%	24%
Pyrexia*	24%	17%
Bone pain*	24%	18%
Vomiting	24%	21%
Anaemia*	23%	19%
Diarrhoea	20%	23%
Dyspnoea	19%	22%
Pain in extremity	22%	20%
Headache	21%	19%
Constipation	20%	17%
AEs reported by <20% of patients but with between-group differences with an unadjusted p<0.05		
Chills	6%	3%
Pain	10%	7%
Renal failure	2.5%	0.2%
Dyspepsia	7%	5%
Lumbar vertebral fracture	5.5%	3%
Increased alanine aminotransferase	5%	3%
Oedema	4%	2%
Hypercalcaemia	3.5%	2%
Metastases to spine	2%	1%
Skin hyperpigmentation	2%	1%
Hyperthermia	1.5%	0.4%
Bronchospasm	1%	0.2%
Increased blood urea	1%	0%
Acute renal failure	1%	0.1%
Toothache	4%	6%
Hypocalcaemia	3%	5.5%

* between-group differences with an unadjusted p<0.05

NR=not reported; NS=not statistically significant

Bone health

In the phase II study,[17] at week 13 and 25, the median percent changes in urinary NTX/creatinine (Cr) among patients with measurable urinary NTX were -73% and -75% for the pooled denosumab groups and -79% and -71% for the IV BP group.

The phase III study reported a greater reduction of bone turnover markers in the denosumab group compared with zoledronic acid.[5] At week 13, the median percent change in urinary NTX/Cr was -80% with denosumab compared with -68% with zoledronic acid (p<0.001) and bone-specific alkaline phosphatase (BSAP) was -44% with denosumab compared with -37% with zoledronic acid (p<0.001).

Skeletal related events

Skeletal related events (SREs), defined in both the trials as pathologic fracture, radiation or surgery to bone or spinal cord compression, were reported in both the phase II and III trials.

By week 25 in the phase II trial, 12% of patients on denosumab and 16% on IV bisphosphonates had experienced at least one SRE. Most of the SREs (85−86%) occurred during the first 13 weeks of the study.[17]

In the 34 month phase III study, median time to first SRE was not reached for the denosumab arm but was 26.4 months for zoledronic acid.[5] The phase III trial reported that, compared to zoledronic acid, denosumab significantly delayed the time to:

- first on-study SRE by 18% (HR 0.82, 95% CI 0.71−0.95, p=0.01)[5]
- first and subsequent SRE by 23% (HR 0.77, 95% CI 0.66−0.89, p=0.001).[5]

The phase III trial also reported that the mean skeletal morbidity rate (defined as the ratio of the number of SREs per patient divided by the patient's time at risk) was reduced in the denosumab group (0.45 events per patient per year) compared to the zoledronic acid group (0.58 events) (p=0.004).[5]

Bone pain

Bone pain was recorded as part of the descriptive summary of adverse events in the phase II trial (see Table 4). By week 57, 12% of patients on denosumab and 19% on IV bisphosphonates had experienced bone pain.[17]

In the phase III trial, 18% of patients on denosumab experienced bone pain compared with 24% of patients on zoledronic acid (p<0.05).[5]

Exploration of the predictive role of baseline NTX levels within a previously reported phase III trial comparing IV zoledronic acid with pamidronate

IV zoledronic acid & urinary NTX levels

An additional paper was identified which reported on a subset analysis from a trial previously included in the Cochrane review. The original trial compared zoledronic acid with pamidronate for breast cancer patients with bone metastases. A subset analysis was conducted in 342 of 1130 patients, for those who were treated with zoledronic acid with NTX assessment information at baseline, 1 month and 3 months available. The subset analysis compared clinical outcomes in patient groups defined by normal (<64 nmol/mmol creatinine) or elevated (≥64 nmol/mmol creatinine) urinary NTX levels at baseline.[18] Here, NTX levels are hypothesized to reflect total bone turnover and burden of skeletal disease as a predictive factor. In addition, in those patients with elevated urinary NTX, comparisons were made between those that then normalised after 3 months on zoledronic acid, to those with persistently elevated NTX.

Overall survival

Median survival duration was longer for patients who had normal NTX levels at baseline (901 days) than for those with elevated NTX levels (719 days), p=0.0068. Patients who had elevated NTX levels at baseline but returned to normal at 3-months had a longer median survival duration of 790 days compared to those with persistently elevated NTX levels of 446 days (RR of death 0.45, 95% CI 0.29−0.70, p=0.0004).[18]

Time to progression

The time to progression of bone disease between patients who had elevated NTX levels at baseline but returned to normal at 3-months and those with persistently elevated NTX levels was not significantly different (p=0.64).[18]

Skeletal related events

Skeletal related events (SREs) were identified as pathologic fractures, spinal cord compression, the need for palliative radiation therapy to the bone, or hypercalcaemia of malignancy. The relative risk ratio for first SRE for those with elevated baseline NTX levels but normal at 3-months compared to those with persistently elevated NTX levels was 0.50 (p=0.0034). The need for radiation therapy to bone was also lower in the elevated than normalised group, compared to the persistently elevated NTX group.[18]

3.3.3 Additional clinical issues of interest

Osteonecrosis of the jaw

A particular adverse event of interest is osteonecrosis of the jaw. While the current systematic review was limited to RCTs investigating bisphosphonates for advanced breast cancer, some additional information relating to bisphosphonates and osteonecrosis of the jaw was identified and reported here.

A taskforce of the American Society for Bone and Mineral Research conducted a review of bisphosphonate-associated osteonecrosis of the jaw (BP ONJ) in 2007.[22] The risk of ONJ in patients with cancer treated with high doses of IV bisphosphonates was reported to be between 1 and 10%. Recommendations were made by the taskforce for patients with malignancy initiating or already receiving bisphosphonate therapy.

Results from a literature review were presented at ECCO 2009 by Walter *et al*[23] on the incidence of BP ONJ. Twenty-seven articles were identified, of which 11 were on breast cancer patients. The average incidence of ONJ in breast cancer patients was reported to be 4.6% (range 1–11%). This appears to be lower than for patients with multiple myeloma (average 7.6%, range 3–21%) or prostate cancer (average 10.3%, range 3–19%). More recently conducted prospective or cross-sectional studies with oral examination provided higher incidences than studies with no oral examination or with a retrospective study design.

In addition, a recently published paper investigated the association between bevacizumab, bisphosphonates and ONJ for patients with advanced breast cancer from two randomised trials and one non-randomised study.[24] In patients treated with bevacizumab, there was a trend towards increased ONJ incidence in those who received bisphosphonate therapy versus those

with no bisphosphonate exposure (0.9 vs. 0.2%, respectively, in the pooled analysis of the randomised trials; 2.4 vs. 0%, respectively, in the non-randomised study).

3.4 Ongoing trials

Two clinical trials registries (Clinical trials.gov: www.clinicaltrials.gov and Current Controlled Trials: www.controlled-trials.com) were searched to identify ongoing randomised controlled trials of bisphosphonates in advanced breast cancer which have not yet published.

Seven ongoing trials were identified (Table 6). Two ongoing trials were identified comparing ibandronate and zoledronic acid (ZICE, SWOG). Four ongoing trials were identified investigating various schedules of zoledronic acid. In addition, another trial was identified which compares bisphosphonates to a different kind of treatment: ibandronate to radiotherapy.

Table 6. Ongoing trials investigating bisphosphonates and advanced breast cancer

Title	Location	Intervention	Comparison	Participants	Outcomes
Zoledronic acid vs. ibandronate					
SWOG-S0308[25] Study has been completed	USA	Oral ibandronate once daily for up to 18 months in the absence of unacceptable toxicity	IV zoledronic acid over 15mins every 4 weeks for up to 18 months in the absence of unacceptable toxicity	N=488 Women with stage IV breast cancer and bone metastases	SREs; pain; adverse events; survival; QoL; performance status
ZICE[26] Ongoing	UK	Oral ibandronate 50mg daily for at least 96 weeks in the absence of disease progression or unacceptable toxicity	IV zoledronic acid 4mg 3–4 weekly for at least 96 weeks in the absence of disease progression or unacceptable toxicity	N= 1400 Patients with newly diagnosed (<3mths) multiple bone metastases from histologically proven breast cancer and considered suitable for treatment with a bisphosphonate	SREs; safety; pain; survival; QoL; cost-efficiency
Schedules					
BISMARK[27] Currently recruiting patients	UK	Standard schedule of zoledronic acid (IV every 3−4 weeks) for 24 months	Marker-directed schedule of zoledronic acid (IV every 3−4,8−9 or 15−16 weeks - based on NTX/creatinine ratio) for 24 months	N=1500 Patients with ABC with radiographic confirmation of bone metastases	Serious related events; QoL; skeletal complications survival; pain; performance status; bone metastases

Title	Location	Intervention	Comparison	Participants	Outcomes
CALGB-70604[28] Currently recruiting patients	USA	Zoledronic acid IV over ≥ 15 minutes. Courses repeat every 4 weeks up to 24 months	Zoledronic acid IV over ≥ 15 minutes. Courses repeat every 12 weeks up to 24 months	N=1538 Patients with metastatic breast cancer, metastatic prostate cancer, or multiple myeloma involving bone	SREs; pain; ONJ; renal dysfunction; performance status
NCT00320710[29] Currently recruiting patients	USA	Zoledronic acid every 4 weeks	Zoledronic acid every 12 weeks	N=705 Confirmed breast cancer with bone metastasis, pretreated with zoledronic acid, or pamidronate or all sequential regimens of both, for a minimum of 9 doses	SRE; safety; bone pain; bone markers
NCT00375427[30] Study has been completed	Italy	Zoledronic acid every 4 weeks	Zoledronic acid every 12 weeks	N=430 Histologically confirmed Stage IV breast cancer with at least one bone metastasis radiologically confirmed. Previous treatment with zoledronic acid every 3−4 weeks, for 9−12 infusions over no more than 15 months	Skeletal Morbidity Rate (SMR); SRE; bone pain
Bisphosphonate vs. radiotherapy					
ISRCTN86185157[31] Study has been completed	UK	Single dose of IV ibandronate over 1–2hrs	Single dose of radiotherapy	N=580 Histologically or cytologically proven underlying primary malignancy of breast, lung or prostate. Bone metastases confirmed radiologically	Bone pain response; QoL; bone morbidity events

CT=computed tomography; IV=intravenous; MR=magnetic resonance; NTX=N-telopeptide of type I collagen; ONJ=osteonecrosis of the jaw; QoL=quality of life; SC=subcutaneous; SRE=skeletal related event

4 Discussion

A limited number of randomised controlled trials investigating bisphosphonates for advanced breast cancer have been published since the Cochrane review update in 2007, which is the primary reference for evidence supporting their use in ABC prior to 2007.

Each trial identified in this review investigated different research questions and/or intervention, therefore comparison between the trials or pooling of results was not possible. Most studies were limited by relatively small number of patients and short treatment and follow-up times. In addition, the primary outcomes measures of some of the identified studies were focussed on bone turnover markers and renal function rather than the pre-specified clinical outcomes of interest for the current review.

Adverse events were reported with more rigour and detail than the earlier bisphosphonate trials which were described in the Cochrane review. The majority of patients (70–95%) in the trials reported at least one adverse event, and serious adverse events were reported by 6%−46% of patients. Some adverse events were reported to be related to underlying disease rather than to treatment. The most commonly reported toxicities for bisphosphonates were nausea and vomiting. Rates of osteonecrosis of the jaw (ONJ) were low in the trials. In the largest study identified (phase III trial: zoledronic acid versus denosumab), the rate of ONJ in the bisphosphonate arm was 1.4%.[5]

Information on quality of life was not reported in any of the RCTs identified.

A small RCT of 44 patients compared the administration of IV zoledronic acid at 11.00am to administration at 11.00pm.[15] This trial is of low clinical relevance given the practical difficulties in administering IV treatment at 11.00pm. Limited results were provided for this trial, however most outcomes (adverse events, bone turnover markers and bone pain) did not differ between treatment arms.

In a single head-to-head RCT with 275 patients, oral ibandronate appeared to have fewer side effects than intravenous zoledronic acid.[16]

Oral ibandronate was preferred over oral clodronate by patients in a small randomised cross-over study reported in abstract form only.[19]

Results from a large trial suggest that denosumab may result in improved outcomes in delaying or preventing skeletal-related events compared to zoledronic acid, with similar toxicity.[5] Denosumab, a monoclonal antibody that binds to RANKL thereby inhibiting osteoclast function and bone resorption, has some potentially beneficial characteristics, including reduction of renal toxicity and acute phase reactions, and convenience of subcutaneous injection.

5 Conclusion

A limited number of randomised controlled trials investigating bisphosphonates for advanced breast cancer have been published since the last update of the Cochrane review[1] in 2007. Various comparisons have been investigated including a head-to-head comparison of oral ibandronate to intravenous zoledronic acid and comparisons between intravenous zoledronic acid and subcutaneous denosumab, a new bone agent. A large trial has suggested that denosumab may result in improved skeletal outcomes compared to zoledronic acid in patients with breast cancer metastatic to bone. The Cochrane review remains the highest quality evidence available to support the use of bisphosphonates in addition to standard anti-cancer therapy in metastatic breast cancer with regards to reduction in risk of skeletal related events. Results from small RCTs with short treatment and follow-up periods indicate that oral ibandronate appears to have fewer side effects than intravenous zoledronic acid and may be preferred by patients to oral clodronate. A number of ongoing trials were identified which are anticipated to provide information regarding the optimal schedule of zoledronic acid, and the relative benefits of oral ibandronate versus zoledronic acid.

Appendix A Contributors

Working group members

The bisphosphonates for advanced breast cancer: a systematic review was developed with input from an expert multidisciplinary Working Group with the following members:

• Dr Nick Pavlakis (Chair)	Medical oncologist
• Ms Denice Bassanelli	Consumer representative
• Ms Sholeh Boyle	Specialist breast nurse
• Dr Roslyn Drummond	Radiation oncologist
• Dr Belinda Kiely	Medical oncologist
• Ms Marlene Parsons	Consumer representative
• Ms Geraldine Robertson	Consumer representative
• A/Prof Andrew Spillane	Surgical oncologist
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National Breast and Ovarian Cancer Centre staff

The following NBOCC staff were involved in the development of the systematic review:

• Ms Katrina Anderson	Project Officer-Research
• Ms Ornella Care	Program Manager
• Dr Karen Luxford	General Manager
• Dr Anne Nelson	Evidence Review & Research Leader
• Ms Rosemary Wade	Senior Project Officer-Research

Appendix B Literature databases searched

Database	Results/Retrievals
Embase	136
Medline	70
Pubmed	71
Cochrane library	1

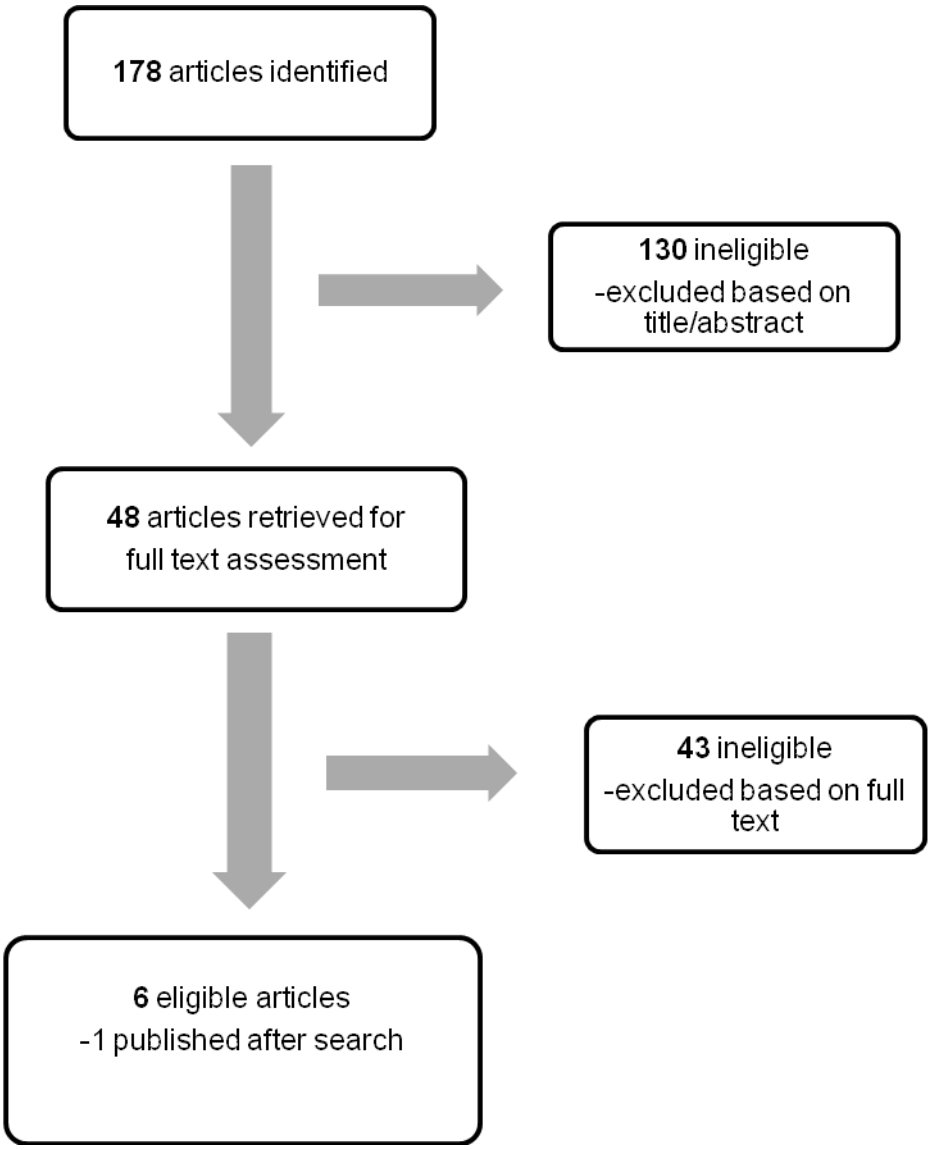
Appendix C Search strategy

Breast cancer	"Breast neoplasms"[MeSH] or (breast and (cancer or carcinoma or tumour or tumor or neoplasm*))
Bisphosphonates	Diphosphonate[MeSH] or bisphosphonate or bisphosphonates or biphosphonate or bisphosphonates or disphosphonate or disphosphonates or diphosphonate or diphosphonates
Randomised controlled trials	Randomized Controlled Trial[MeSH] or "randomized controlled trial" or "randomized controlled trials" or "randomised controlled trial*" or "random*" or "random allocation" or "controlled clinical trial" or "controlled trial" or "double blind method" or "single blind method" or "metaanalysis[MeSH]" or "meta-analysis" or "meta analysis" or "systematic review" or "pooled analysis"

Appendix D Guideline and clinical trial sites searched

Acronym	Organisation	Website
CCO	Cancer Care Ontario	http://www.cancercare.on.ca/
ESMO	European Society of Medical Oncology	http://www.esmo.org/
GIN	Guidelines International Network	http://www.g-i-n.net/
NCCN	National Comprehensive Cancer Network	http://www.nccn.org/index.asp
NGC	National Guideline Clearinghouse	http://www.guideline.gov/
NICE	National Institute for Health and Clinical Excellence	http://www.nice.org.uk/
SIGN	Scottish Intercollegiate Guidelines Network	http://www.sign.ac.uk/
	ClinicalTrials.gov	http://www.clinicaltrials.gov/
	Current Controlled Trials	http://www.controlled-trials.com

Appendix E Flowchart of inclusion/exclusion for literature review



Abbreviations

ABC	advanced breast cancer
AE	adverse event
ALP	alkaline phosphatise
ANZBMS	Australia and New Zealand Bone and Mineral Society
ASBMR	American Society for Bone and Mineral Research
ASCO	American Society of Clinical Oncology
BP	bisphosphonate
BSAP	bone-specific alkaline phosphatase
CCO	Cancer Care Ontario
CECOG	Central European Cooperative Oncology Group
CI	confidence interval
CTX	cross-linked C-terminal telopeptide of type I collagen
ECCO	European Cancer Organisation
ESMO	European Society for Medical Oncology
HR	hazard ratio
ITT	intention-to-treat
IV	intravenous
MBD	metastatic bone disease
NBOCC	National Breast and Ovarian Cancer Centre
N-BP	nitrogen-containing bisphosphonate
NCCN	National Comprehensive Cancer Network
NICE	National Institute for Health and Clinical Excellence
NTX	N-telopeptide of type I collagen
OC	osteocalcin
ONJ	osteonecrosis of the jaw
PINP	amino-terminal procollagen propeptides to type I collagen

PTH	parathyroid hormone
QoL	quality of life
RANKL	receptor activator of nuclear factor kappa-B ligand
RCT	randomised controlled trial
RR	relative risk
SABCS	San Antonio Breast Cancer Symposium
SC	subcutaneous
SIGN	Scottish Intercollegiate Guideline Network
SRE	skeletal related event
ZA	zoledronic acid

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