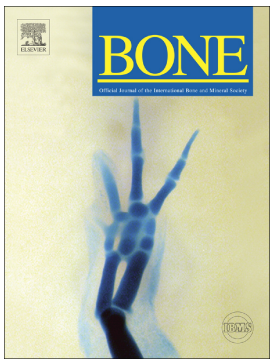

Article:
Coleman, R. orcid.org/0000-0002-4275-1043 (2020) Bisphosphonates and breast cancer – from cautious palliation to saving lives. Bone, 140. 115570. ISSN 8756-3282

https://doi.org/10.1016/j.bone.2020.115570



Bisphosphonates and breast cancer – From cautious palliation to saving lives

Robert Coleman

PII: S8756-3282(20)30350-1

DOI: https://doi.org/10.1016/j.bone.2020.115570

Reference: BON 115570

To appear in: *Bone*

Received date: 12 May 2020

Revised date: 13 July 2020

Accepted date: 28 July 2020

Please cite this article as: R. Coleman, Bisphosphonates and breast cancer – From cautious palliation to saving lives, *Bone* (2020), https://doi.org/10.1016/j.bone.2020.115570

Bisphosphonates and breast cancer – From cautious palliation to saving lives

Robert Coleman,

Mellanby Centre for Bone Research,

Department of Oncology and Metabolism,

University of Sheffield.

Address for correspondence: r.e.coleman@sheffield.ac.uk

Abstract

Bone metastases are common in breast cancer and may cause considerable morbidity including fractures, severe pain, nerve compression and hypercalcaemia. Alongside developments in the multidisciplinary management for patients with metastatic breast cancer, the use of bisphosphonates, and more recently denosumab, has transformed the course of advanced breast cancer for many patients resulting in a major reduction in skeletal complications, reduced bone pain and improved quality of life. Additionally, because the bone marrow microenvironment is so intimately involved in the metastatic processes required for cancer dissemination, the use of adjuvant bisphosphonates has been studied extensively over the past 25 years in many randomised trials. We now have clear evidence that bisphosphonates significantly reduce both metastasis to bone and mortality in postmenopausal women with early breast cancer. Efficacy seems similar across different biological subgroups of postmenopausal breast cancer with the use of either a nitrogen-containing bisphosphonate such as intravenous zoledronate or daily oral ibandronate as well as the non-nitrogen containing agent, daily oral clodronate. In this overview of evolving role of bisphosphonates in breast cancer, focussing particularly on pamidronate and zoledronate, the long winding development road from the 1970s through to the present day is described and some of the serendipitous findings, "lucky breaks" and regulatory decisions along the way outlined.

Highlights

Bisphosphonates have transformed the care of breast cancer patients with bone metastases and are firmly established as a key element of standard treatment throughout the course of the disease.

In postmenopausal women with early breast cancer, bisphosphonates reduce bone recurrences by about one quarter and cancer deaths by one sixth.

Due to limited understanding of the underlying biology of metastasis and the limitations of animal model systems, the clinical development of bisphosphonates in oncology has been relatively slow and complex and largely reliant on discoveries and innovation from academic groups rather than "big pharma".

Introduction

Bisphosphonates were first synthesised in the late 19th century, but initial usage was restricted to a range of industrial processes and their potential clinical relevance not appreciated until the late 1960s.[1] Then, following a greater understanding of their pharmacology[2,3] and evaluation of the first available oral agents such as etidronate[4] and clodronate[5] for the treatment of osteoporosis and Paget's disease of bone, a few academic groups, particularly in Europe including Helsinki (Elomaa), Sheffield (Kanis, Russell), Leiden (Bjjvoet, Papapoulos), Brussels (Body), London (Rubens, Coleman), Manchester (Howell, Anderson) and Lausanne (Burckhardt, Thurlimann), began to investigate the potential role of bisphosphonates in cancer patients.

Hypercalcaemia of malignancy

The initial focus was through studies of bisphosphonates for the treatment of hypercalcaemia of malignancy which, 30 years ago, was a relatively common, life threatening metabolic complication of advanced cancer. Treatments available at the time, such as calcitonin, mithramycin and corticosteroids, in addition to intravenous rehydration, were all sub-optimal and typically only controlled serum calcium for a few days. As a result, there was a major unmet clinical need for a safe and effective treatment strategy for hypercalcaemia of malignancy.

The first trials utilised etidronate[6] and clodronate[7,8] with some success but the restoration of normocalcaemia was sub-optimal and short-lived. Initially, there were concerns that potent intravenous bisphosphonates, such as pamidronate (often referred to as APD in the 1980s and 90s),[9] would cause renal damage and for this reason, experience was limited to the daily administration of very low doses (pamidronate 1mg), alongside vigorous intravenous hydration, given until the calcium normalised.[10] Subsequently during the 1980s, several oncology research teams, including myself as a young research fellow at the time, cautiously and on the back of warnings from Olaf Bijvoet and colleagues with considerable trepidation, tested larger single doses of 5mg, 15mg and 30mg in patients with hypercalcaemia. Fortunately, significant renal adverse events were not seen and these single treatments were shown to be both safe and effective, restoring normocalcaemia in around three quarters of treated patients for a median duration of 2-3 weeks.[11,12] Some years later, regulatory approval in both Europe and North America of pamidronate at doses of 60-90mg[13] as a single infusion was granted and almost overnight, alongside intravenous fluids, the standard of care for hypercalcaemia of malignancy was changed.

Prevention of skeletal morbidity in metastatic breast cancer

In the 1980s, small trials with oral clodronate[14] and oral pamidronate[15] had also suggested useful effects on skeletal morbidity in breast cancer. The small trial from

the group led by Inkeri Elomaa in Finland even suggested a survival benefit from the use of daily oral clodronate in women with metastatic bone disease,[14] although this was probably just a chance observation associated with the small number of patients included in the study. However, excited by these preliminary results, and despite any meaningful commercial interest from the pharmaceutical industry which at that time was not seriously considering a role for bisphosphonates in malignant disease, a number of European investigators tested intermittent intravenous pamidronate as a palliative treatment approach in women with bone metastases from breast cancer.[16-19] In these studies heavily pre-treated patients with metastatic bone disease received infusions of pamidronate without background endocrine or cytotoxic treatments and the effects on bone imaging, bone biomarkers and pain observed in much the same way as one would in a phase II study evaluating efficacy of a more conventional anticancer treatment.

Our early experience at Guy's Hospital in the first of these studies showed clinically useful effects on bone pain from metastatic disease with pamidronate 30mg administered every two weeks.[16] In addition, two of the first few patients treated were noted to have developed radiographic sclerosis of lytic metastatic lesions on follow-up radiographs. At the time the imaging response was interpreted as a possible anti-tumour effect of the bisphosphonate resulting in the healing of osteolytic bone metastases, created considerable international interest in this novel approach to the treatment of bone metastases, and encouraged recruitment to the ongoing studies within Europe.[17-19] With hindsight however, this interpretation was almost certainly not correct, but rather reflected the consequences of the uncoupling of bone resorption and formation with specific inhibition of tumour induced osteolysis by pamidronate alongside continued increased new bone formation.

Initially Ciba Geigy, the manufacturer of pamidronate at the time, had little interest in the commercial development of pamidronate. However, following the publication of our experience and other pilot studies in advanced breast cancer confirming the beneficial effects of pamidronate on pain from bone metastases,[16,19] the company initiated large randomised clinical trials in the early 1990s. These evaluated the effects of intravenous pamidronate every 3-4 weeks on a new endpoint termed skeletal related events (SREs) proposed by the company to try and objectively measure the effects of treatment on the skeletal morbidity associated with metastatic bone disease in breast cancer[20,21] or myeloma bone disease.[22] SREs included radiotherapy to bone for pain relief or structural damage, pathological fracture, spinal cord compression, orthopaedic intervention for impending or actual fracture and hypercalcaemia and were accepted by the regulatory authorities as appropriate endpoints for registration studies and regulatory approval.

These large phase III studies, conducted largely in the United States,[20-22] and a similar trial with oral clodronate,[23] showed significant benefits in breast cancer with a 25-30% reduction in risk of SREs over and above standard anticancer and supportive care treatments, and associated with an improvement in bone pain, reduced analgesic consumption and improved quality of life.[20-22]

The evaluation of these studies by the regulators in the United States are of historic interest and perhaps illustrate the relative subjectivity of the regulatory processes at the time. In the studies with pamidronate, the benefits in terms of reducing the proportion of patients experiencing an SRE were particularly striking in the patients treated with chemotherapy[20] and the Oncology Drugs Advisory Committee ODAC) had no problem recommending regulatory approval to the Food and Drugs Administration (FDA). However, the primary endpoint data in patients receiving endocrine treatment,[21] while consistent with the findings in the chemotherapy treated cohort, were only of borderline statistical significance and ODAC was uncertain and split 3-3 on whether to recommend approval[24] until a patient advocate on the panel urged the committee to reconsider on the basis that the treatment had relatively few side effects and appeared to make a large difference to endpoints that really matter to patients such as pain, quality of life and mobility. It seemed likely that her viewpoint was influenced by the descriptions of significant toxicity associated with the use of a chemotherapy agent, irinotecan, she had listened to earlier in the day. Despite the challenging and significant toxicity alongside only modest efficacy, ODAC had recommended accelerated approval of irinotecan. On reflection ODAC agreed with the patient advocate and, as a result of these two trials, intravenous pamidronate became part of standard management for patients with bone involvement from breast cancer, irrespective of the underlying systemic treatment. One wonders what might have happened if the order of the hearings at ODAC that day had been reversed!

For clodronate the outcome was less successful. Despite the benefits demonstrated by several academic teams of trialists,[14,23,25] approval in the United States was not recommended due to a handful of isolated reports of leukaemia developing in patients who had at some time in their clinical course been treated with clodronate. The fact that these patients had received many other treatments, including those such as melphalan and radiation therapy that are known be carcinogenic, was not sufficient to sway the views of the regulators and to this day, although approved in Europe, Canada and many other parts of the world, clodronate does not have a licence within the United States for any therapeutic indication.

In the late 1990s, more potent bisphosphonates including ibandronate (oral and intravenous)[26,27] and zoledronate[28] were developed. Zoledronate is commonly, but inappropriately, called zoledronic acid in an attempt to distinguish it from other bisphosphonates. However, at physiological pH it, and all other bisphosphonates,

present as anions and not as free acids. Interestingly, potency in laboratory systems provided only marginal benefits in the clinic beyond the ability to lower the dose administered and, due more to the long biological half-life in bone rather than potency *per se*, extend the interval between treatments. Development of zoledronate also began in Europe for hypercalcacaemia[29] before evaluation for prevention of skeletal morbidity from bone metastases.[30] Oral ibandronate provides a particularly useful alternative for patients wishing to avoid treatment by injection[26] although in a large randomised study comparing zoledronate and oral ibandronate, non-inferiority of the oral option could not be proven.[31]

In the large phase III registration trials, zoledronate was compared to pamidronate in patients with breast cancer and multiple myeloma[32] as this was the standard of care at the time and compared to placebo in prostate cancer[33] and other solid tumours.[34] In the breast cancer study, zoledronate was statistically "non-inferior" to pamidronate[32] and, on this basis, was approved by the regulatory agencies worldwide for routine clinical use. Again, the regulatory process in the United States was interesting. Although the more cautious endpoint of non-inferiority was the primary endpoint of the study, the expectation was that the added potency of zoledronate would result in superior outcomes with clear benefit in reducing the numbers of patients experiencing SREs and prolonging the time to the first SRE. However, these outcomes were very similar with the two treatments and the discussions with the regulators focussed on validity of the non-inferiority margin previously agreed with the FDA as the primary endpoint. This required that the 95% confidence intervals for the comparative hazard ratio between the two treatments excluded the loss of more than 50% of the benefit achieved with pamidronate in the original pamidronate versus placebo studies. Debate as to whether this was sufficiently strict (modern non-inferiority trials require preservation of a much greater proportion of the standard treatment effect) and whether the populations studied were comparable ensued. In the end ODAC were satisfied that the findings from the breast cancer trial were meaningful and valid and recommended approval for use in this indication as well as other solid tumours (Table 1).[35]

Longer follow-up of patients in the trial comparing zoledronate to pamidronate, coupled with the use of exploratory complex multiple event analyses, showed statistically significant superiority of zoledronate over pamidronate for breast cancer patients with a 20% reduction in the overall risk of SREs[36] and zoledronate became the standard of care throughout most of the world for patients with breast cancer and bone metastases based more in most centres on the convenience of a short infusion time rather than because of the marginal greater efficacy.

Subsequently denosumab was introduced with much of the early development work led from Europe.[37] In the phase III registration trials, denosumab was shown to be marginally more effective in reducing skeletal morbidity[38] such that the rate of SREs

observed in the pre-bisphosphonate era of 3-4 per year has now fallen to <1 per year. Additionally, the severity of the residual SREs that do occur is generally mild with very few episodes nowadays of spinal cord compression, long bone fracture or hypercalcaemia in the context of metastatic breast cancer.[39]

As a class, bisphosphonates (and indeed denosumab also) are well tolerated and the risk-benefits clearly favour use in metastatic bone disease, However, following case reports in 2003[40] and subsequent small case series of patients[41] developing osteonecrosis of the jaw (ONJ) associated with the use of a bisphosphonate, a degree of hysteria developed surrounding this adverse event. For a time, fear of ONJ threatened to limit the use of these important treatments. However, with careful monitoring of patients, good oral and dental health and minimising of surgical procedures on the jaw and dental extractions,[42] the risk of developing ONJ with the relatively intensive dosing schedules used in advanced cancer is low at around 1% per year on treatment,[43] and considerably less than this for patients receiving bisphosphonates in the adjuvant setting or to prevent treatment induced bone loss.[44,45] Such risks are clearly dwarfed by the 30-50% reduction in SRE and most breast cancer patients and their treating specialists recognise the benefits and accept the small level of risk for ONJ associated with treatment.

Metastasis prevention

Because of their profound effects on bone physiology, there has been interest for several decades in the potential use of bisphosphonates to modify the process of metastasis and have effects on important clinical outcomes such as disease recurrence and survival.[46] The potential benefits of bone-targeted treatments on the clinical course of breast cancer have been the subject of clinical trials for more than 20 years.

Ingo Diel and colleagues published the first meaningful randomised trial of adjuvant bisphosphonates in early breast cancer in 1998.[47] Patients were selected on the basis of the presence of disseminated tumour cells (DTC) in bone marrow aspirates taken at the time of surgery but without overt metastases identified on imaging tests. Patients with DTC detected by immunocytochemistry have a relatively poor prognosis with 2-3 times increased risk for subsequent relapse compared with DTC negative patients.[48] In their randomised trial, Diel and colleagues showed fewer relapses, especially in bone and improved survival in the patients treated with daily oral clodronate. Similar positive findings with oral clodronate were reported a few years later by Trevor Powles and colleagues in a larger placebo-controlled trial.[49] However a study from Finland reported a possible adverse effect of clodronate on outcomes.[50] These varying results were at the time somewhat difficult to reconcile and prevented approval of clodronate as an adjuvant treatment strategy.

In 2009, more than a decade later, a potentially practice changing study conducted by the Austrian Breast Cancer Study Group (ABCSG)-12 was reported. This academic study showed significant benefit from the addition of six monthly zoledronate when added to endocrine therapy that included ovarian suppression for premenopausal women with oestrogen receptor (ER) positive disease.[44] For the first time, breast oncologists started to take an interest in the concept of modifying the host microenvironment as an alternative or addition to conventional tumour cell directed therapies such as chemotherapy and targeted treatments such as endocrine treatments for ER+ disease and trastuzumab for HER2+ disease. Indeed, the ABCSG-12 study was perhaps over-interpreted and some oncologists started, without regulatory approval, to recommend the use of adjuvant bisphosphonates in their young women with breast cancer, focussing on the fact that the study participants were premenopausal at diagnosis but ignoring the fact that they were all rendered postmenopausal through the use of ovarian suppression therapy. However, a year later, the first results from the larger AZURE study[51] brought that to a sudden stop.

The AZURE study had been designed by a team of international investigators led from the University of Sheffield. The trial was funded through an unrestricted grant from Novartis and run as an academic study. The study had much broader inclusion criteria than ABCSG-12, including pre and postmenopausal women and both ER+ and ER- stage II/III breast cancer. It also utilised a more intensive treatment regimen of zoledronate with 3-4 weekly infusions for the first 6 treatments, typically administered alongside adjuvant chemotherapy, followed by a maintenance dose every 3-6 months for 5 years resulting in a total of 19 infusions of zoledronate 4mg. Somewhat surprisingly in light of the ABCSG-12 findings and most of the experience with daily oral clodronate, the study showed no benefit on recurrence or survival in an intention to treat (ITT) analysis either at the time of the initial analysis[51] or at later planned follow-up analyses.[52] However, the AZURE study did identify potential benefits in a pre-defined subgroup of patients who were postmenopausal at the time of study entry and, taken with the benefits seen in ABCSG-12 and several bone protection studies[44,45,53] conducted in postmenopausal women, suggested that any benefits associated with the use of adjuvant bisphosphonates were perhaps restricted to women who had low levels of reproductive hormones due to either natural age related menopause or ovarian function suppression.

This hypothesis was supported by studies in mouse models of metastasis in which the reduction in metastasis and survival of animals treated with zoledronate were much greater in mice that had previously undergone oophorectomy.[54] In an initiative co-ordinated by the Early Breast Cancer Clinical Trials Group (EBCTCG) to investigate this hypothesis in patients, data from randomised trials that had evaluated the effect of an adjuvant bisphosphonate on breast cancer outcomes were collated from trialists around the world. As a result of this endeavour it was possible to perform a

detailed individual patient meta-analysis of 18,766 women included in a total of 36 randomised trials comparing the administration of a bisphosphonate (any type and duration) versus none in women with early breast cancer.[55] A total of 3,453 breast cancer recurrences and 2,106 breast cancer deaths were available, enabling the meta-analysis to demonstrate important clinical benefits that could not be reliably identified in individual trials.

The meta-analysis showed overall (Figure 1), including all randomised patients, that bisphosphonates reduced first distant recurrence in bone (risk ratio (RR)=0.83; 95%CI 0.73-0.94, 2p=0.004) and confirmed a significant interaction between treatment efficacy and menopausal status. There were no demonstrable benefits in any disease outcome seen in the 6,171 premenopausal women but, in the 11,767 postmenopausal women, highly significant and clinically important reductions in bone recurrence (RR=0.72; 95%CI 0.60-0.86, 2p=0.0002) and breast cancer mortality (0.82; 95%CI 0.73-0.93, 2p=0.002) with follow-up out to 10 years after randomisation were seen.[55] Benefits appeared to be of similar magnitude across different biological subgroups of breast cancer (ER + and ER-) and independent of the bisphosphonate used in the trials which included daily oral clodronate, daily oral ibandronate and intermittent intravenous zoledronate. However, there are no randomised data available on the efficacy of osteoporosis dosing of alendronate or risedronate and extrapolation of the effects to these low dose oral schedules is not possible.

The mechanisms underlying the relationships between metastasis prevention and ovarian function are not well understood. Preliminary data, however, indicate that the efficacy of adjuvant bisphosphonates may be related to the expression of the transcription factor MAF within the primary tumour. In the AZURE trial, highly significant improvements in recurrence and survival with zoledronate were seen in the 80% of patients with MAF negative tumours (irrespective of menopausal status) while in the 20% with over-expression of MAF, worse outcomes were seen especially in young patients who were still menstruating at the start of treatment.[56,57] MAF regulates many processes of potential relevance to metastasis including adhesion molecules, PTHrP and the activity of $\gamma\Delta$ T lymphocytes.[57,58] Validation of these observations are ongoing.

The reduction in 10-year breast cancer mortality equates to around 10,000 lives saved within the 28 European Union countries. Despite the lack of regulatory approval for bisphosphonate use in the setting of early breast cancer, these findings are changing clinical practice and, increasingly, the use of adjuvant bisphosphonates is now recommended in clinical guidelines both in Europe and North America and, in many centres, become part of routine adjuvant therapy for postmenopausal women with early breast cancer deemed at intermediate to high risk for recurence.[59,60]

The potential disease modifying effects of denosumab have also been assessed in early breast cancer. The osteoporosis dosing schedule of denosumab was evaluated

in the ABCSG-18 study that was designed primarily to assess the ability of denosumab to prevent fractures associated with the use of aromatase inhibitors in ER+ postmenopausal women with breast cancer.[61] A significant improvement in disease-free survival with denosumab was reported, but this was mainly due to reductions on second non-breast primary cancers and deaths without recurrence rather than prevention of breast cancer recurrences; observations that seem biologically implausible.

In the DCARE trial, 4509 women with early breast cancer at moderate to high risk for recurrence were randomised to receive either denosumab or placebo, but using a more intensive treatment schedule than in the ABCSG-18 study of denosumab 120mg every 3-4 weeks for 6 months and then continued every 3 months for a total duration of 5 years.[62] Denosumab had no significant effect on the primary endpoint of bone metastasis free survival (HR=0·97, 95%CI 0·82–1·14; p value=0·70). Additionally, disease-free and overall survival were unaffected by the addition of denosumab to standard adjuvant breast cancer treatments, either in the study population as a whole or in the postmenopausal subgroup; findings that clearly contrasted to those seen with adjuvant bisphosphonates. The apparent differences between adjuvant denosumab and bisphosphonates suggest that the benefits of the latter perhaps relate more to their broader biological effects on other aspects of the metastatic process rather than their primary effects on bone cell function. Effects on tumour cell adhesion and migration, angiogenesis and immune effects in animal models, as well as clearing of DTC from the bone marrow with bisphosphonates, have all been demonstrated.[46] On the other hand, any effects denosumab might have on tumour cells would likely be restricted to RANK-expressing cells which constitute only a small proportion of breast cancers.[63]

Finally, the knowledge obtained from studies of bone-targeted treatments in osteoporosis has been applied to the cancer setting. Many patients, notably breast cancer patients receiving aromatase inhibitors or experiencing chemotherapy induced premature menopause experience rapid bone loss due to the resultant suppression of circulating oestradiol levels and are at increased risk of fragility fractures. Both bisphosphonates[45,53] and denosumab[64] have been shown to prevent this treatment induced bone loss; the effects of denosumab on fracture incidence were particularly impressive with a 50% reduction in fracture risk.[64]

In conclusion, the use of bisphosphonates has had profound beneficial effects on the clinical course of breast cancer, preventing recurrence in some situations and reducing skeletal morbidity and the clinical consequences of metastatic bone disease for those with incurable advanced disease. However, the development pathway has been long, somewhat tortuous and, at times, unconventional, reliant largely on academic innovation at a time when drug development was less structured and rigid. Academic partnerships with the pharmaceutical industry have been important and

necessary but, much of what we have learnt over the past 30 years might not have occurred under the current approach of tightly focussed and rigid pharma-driven drug development.

References

1. Francis MD, Russell RG, Fleisch H. Diphosphonates inhibit formation of calcium phosphate crystals in vitro and pathological calcification in vivo. Science. 1969; 165(3899):1264-1266.
2. Russell RG. Bisphosphonates: the first 40 years. Bone. 2011 Jul;49(1):2-19.
3. Cremers S, Drake MT, Ebetino FH, Bilezikian JP, Russell RGG. Pharmacology of bisphosphonates. Br J Clin Pharmacol. 2019 Jun;85(6):1052-1062.
4. Watts NB, Chesnut CH, Genant HK, et al. History of etidronate. Bon**e** 2020; 134,115222
5. Douglas DL, Duckworth T, Russell RG, Kanis JA, Preston CJ, Preston FE, Prenton MA, Woodhead JS. Effect of dichloromethylene diphosphonate in Paget's disease of bone and in hypercalcaemia due to primary hyperparathyroidism or malignant disease. Lancet. 1980 May 17;1(8177):1043-7.
6. Hasling C, Charles P, Mosekilde L. Etidronate disodium in the management of malignancy-related hypercalcemia. Am J Med. 1987 Feb 23;82(2A):51-4.
7. Jung A, Chantraine A, Donath A, et al. Use of dichloromethylene diphosphonate in metastatic bone disease. N Engl J Med. 1983 Jun 23;308(25):1499-501
8. Percival RC, Paterson AD, Yates AJ, et al. Treatment of malignant hypercalcaemia with clodronate. Br J Cancer. 1985 May;51(5):665-9.
9. Papapoulos S. Pamidronate: A model compound of the pharmacology of nitrogen containing bisphosphonates; A Leiden historical perspective Bone 134 (2020) 115244
10. Sleeboom HP, Bijvoet OL, van Oosterom AT, Gleed JH, O'Riordan JL. Comparison of intravenous (3-amino-1-hydroxypropylidene)-1, 1-bisphosphonate and volume repletion in tumour-induced hypercalcaemia. Lancet. 1983; 2(8344):239-243.
11. Coleman R.E. & Rubens R.D. 3(amino-1.1-hydroxypropylidene) bisphosphonate (APD) for hypercalcaemia of breast cancer. Br J Cancer 1987; 56: 465-469.
11. Body JJ, Borkowski A, Cleeren A, Bijvoet OL. Treatment of malignancy-associated hypercalcemia with intravenous aminohydroxypropylidene diphosphonate J Clin Oncol 1986 Aug;4(8):1177-83.
12. Gucalp R, Theriault R, Gill I, et al. Treatment of cancer-associated hypercalcemia. Double-blind comparison of rapid and slow intravenous infusion regimens of pamidronate disodium and saline alone. Arch Intern Med. 1994; 154(17):1935-1944.
13. Elomaa I, Blomqvist C, Gröhn P, et al. Long-term controlled trial with diphosphonate in patients with osteolytic bone metastases. Lancet. 1983; 1(8317):146-149.
14. van Holten-Verzantvoort AT, Bijvoet OL, Cleton FJ, et al. Reduced morbidity from skeletal metastases in breast cancer patients during long-term bisphosphonate (APD) treatment. Lancet. 1987; 2(8566):983-985.
15. Coleman R.E., Woll P.J., Miles M., Scrivener W., Rubens R.D. Treatment of bone metastases from breast cancer with (3-amino-1-hydroxypropylidene)-1.1-biphosphonate (APD). Br J Cancer, 1988; 58:621-625.

16. Morton AR, Cantrill JA, Pillai GV, et al. Sclerosis of lytic bone metastases after disodium aminohydroxypropylidene bisphosphonate (APD) in patients with breast carcinoma. BMJ. 1988 Sep 24;297(6651):772-3.

17. Thiébaud D, Leyvraz S, von Fliedner V, et al. Treatment of bone metastases from breast cancer and myeloma with pamidronate. Eur J Cancer. 1991;27(1):37-41.

18. Thürlimann B[1], Morant R, Jungi WF, Radziwill A. Pamidronate for pain control in patients with malignant osteolytic bone disease: a prospective dose-effect study. Support Care Cancer. 1994 Jan;2(1):61-5.

19. Hortobagyi GN, Theriault RL, Lipton A et al. Long-term prevention of skeletal complications of metastatic breast cancer with pamidronate: Protocol 19 Aredia Breast Cancer Study Group. J Clin Oncol 1998; 16: 2038-2044.

20. Theriault RL, Lipton A, Hortobagyi GN et al. Pamidronate reduces skeletal morbidity in women with advanced breast cancer and lytic bone lesions: a randomized, placebo-controlled trial. Protocol 18 Aredia Breast Cancer Study Group. J Clin Oncol 1999; 17: 846–854.

21. Berenson JR, Lichtenstein A, Porter L, et al. Efficacy of pamidronate in reducing skeletal events in patients with advanced multiple myeloma. N Engl J Med 1996; 334:488-493.

22. Paterson AH, Powles TJ, Kanis JA, McCloskey E, Hanson J, Ashley S. Double-blind controlled trial of oral clodronate in patients with bone metastases from breast cancer. J Clin Oncol. 1993; 11(1):59-65.

23. https://www.cancernetwork.com/breast-cancer/odac-recommends-approval-aredia-breast-cancer-bone-mets

24. Martoni A, Guaraldi M, Camera P, et al. Controlled clinical study on the use of dichloromethylene diphosphonate in patients with breast carcinoma metastasizing to the skeleton. Oncology. 1991;48(2):97-101.

25. Body, J. J. et al. Oral ibandronate reduces the risk of skeletal complications in breast cancer patients with metastatic bone disease: results from two randomised, placebo-controlled phase III studies. Br. J. Cancer 2004; 90, 1133–1137.

26. Body JJ, Diel IJ, Lichinitser MR, et al. Intravenous ibandronate reduces the incidence of skeletal complications in patients with breast cancer and bone metastases. Ann Oncol. 2003; 14(9):1399-405.

27. Reid I, Green JR, Lyles KW et al. Zoledronate Bone 2020;134, 115390

28. Barrett-Lee P, Casbard A, Abraham J et al. Oral ibandronic acid versus intravenous zoledronic acid in treatment of bone metastases from breast cancer: a randomised, open label, non-inferiority phase 3 trial. Lancet Oncol 2014; 15: 114-122.

29. Berenson JR., Rosen LS., Howell A., et al. Zoledronic acid reduces skeletal-related events in patients with osteolytic metastases Cancer 91/7: 1191-1200, 2001

30. Body JJ, Lortholary A, Romieu G, Vigneron AM, Ford J. A dose-finding study of zoledronate in hypercalcemic cancer patients. J Bone Miner Res. 1999 Sep;14(9):1557-61.

31. Rosen LS, Gordon D, Kaminski M et al. Zoledronic acid versus pamidronate in the treatment of skeletal metastases in patients with breast cancer or osteolytic lesions of multiple myeloma: a phase III, double-blind, comparative trial. Cancer J. 2001; 7(5): 377-387

32. Saad, F. et al. A Randomized, Placebo-Controlled Trial of Zoledronic Acid in Patients With Hormone-Refractory Metastatic Prostate Carcinoma. JNCI J. Natl. Cancer Inst. 2002; 94, 1458–1468.

33. Rosen, L. S. et al. Long-term efficacy and safety of zoledronic acid in the treatment of skeletal metastases in patients with nonsmall cell lung carcinoma and other solid tumors. Cancer 2004; 100, 2613–2621.

34. https://www.cancernetwork.com/breast-cancer/odac-recommends-fda-approve-zometa-bone-metastases

35. Rosen LS, Gordon D, Kaminski M, et al. Long-term efficacy and safety of zoledronic acid compared with pamidronate disodium in treatment of skeletal complications in patients with advanced multiple myeloma or breast cancer: a randomized, double-blind, multicenter, comparative trial. Cancer 2003; 98:1735-1744.

36. Body JJ, Facon T, Coleman RE, et al. A study of the biological receptor activator of nuclear factor-kappab ligand inhibitor, denosumab, in patients with multiple myeloma or bone metastases from breast cancer. Clin Cancer Res. 2006 Feb 15;12(4):1221-8.

37. Stopeck AT, Lipton A, Body JJ, et al. Denosumab compared with zoledronic Acid for the treatment of bone metastases in patients with advanced breast cancer: a randomized, double-blind study. J Clin Oncol 2010; 28: 5132-5139.

38. von Moos R, Costa L, Gonzalez-Suarez E et al. Management of bone health in solid tumours: from bisphosphonates to a monoclonal antibody. Cancer Treatment Reviews 2019; 76: 57-67

39. Marx RE. Pamidronate (Aredia) and zoledronate (Zometa) induced avascular necrosis of the jaws: a growing epidemic. J Oral Maxillofac Surg. 2003 Sep;61(9):1115-7.

40. Ruggiero SL, Mehrotra B, Rosenberg TJ, Engroff SL. Osteonecrosis of the jaws associated with the use of bisphosphonates: a review of 63 cases. J Oral Maxillofac Surg. 2004 May;62(5):527-34.

41. Saad, F., Brown JE, Van Poznak C et al. Incidence, risk factors, and outcomes of osteonecrosis of the jaw: integrated analysis from three blinded active-controlled phase III trials in cancer patients with bone metastases. Ann. Oncol. 2012; 23, 1341–1347.

42. Nicolatou-Galitis, O. Schiodt M, Mendes R et al. Medication-related osteonecrosis of the jaw: definition and best practice for prevention, diagnosis, and treatment. Oral Surg. Oral Med. Oral Pathol. Oral Radiol. 2019; 127, 117–135.

43. Gnant M, Mlineritsch B, Schippinger W, et al.: Endocrine therapy plus zoledronic acid in premenopausal breast cancer. N Engl J Med. 2009, 360:679-691.

44. Brufsky A, Harker WG, Beck JT, et al. Final 5-year results of Z-FAST trial: adjuvant zoledronic acid maintains bone mass in postmenopausal breast cancer patients receiving letrozole. Cancer 2012; 118,1192-1201.

45. Coleman R, Gnant M, Morgan G, Clezardin P. Effects of bone-targeted agents on cancer progression and mortality. J Nat Cancer Inst 2012; 104: 1059-1067

46. Diel IJ, Jaschke A, Solomayer EF, et al.: Adjuvant oral clodronate improves the overall survival of primary breast cancer patients with micrometastases to the bone marrow: a long-term follow-up. Annals of Oncology 2008, 19:2007-2011.

47. Liang DH, Hall C, Lucci A. Circulating Tumor Cells in Breast Cancer. Recent Results Cancer Res. 2020;215:127-145

48. Powles T, Paterson A, McCloskey E, et al.: Reduction in bone relapse and improved survival with oral clodronate for adjuvant treatment of operable breast cancer [ISRCTN83688026]. Breast Cancer Research *: BCR.* 2006, *8:*R13.

49. Saarto T, Vehmanen L, Virkkunen P, Blomqvist C.Ten-year follow-up of a randomized controlled trial of adjuvant clodronate treatment in node-positive breast cancer patients. Acta Oncol. 2004;43(7):650-6.

50. Coleman RE, Marshall H, Cameron D, et al.: Breast-cancer adjuvant therapy with zoledronic acid. N Engl J Med*.* 2011, *365:*1396-1405.

51. Coleman RE, Collinson M, Gregory W, et al. Benefits and risks of adjuvant treatment with zoledronic acid in stage II/III breast cancer. 10 years follow-up of the AZURE randomized clinical trial (BIG 01/04). J Bone Oncol. 2018 Sep 27; 13,123-135

52. Coleman R, de Boer R, Eidtmann H, et al.: Zoledronic acid (zoledronate) for postmenopausal women with early breast cancer receiving adjuvant letrozole (ZO-FAST study): final 60-month results. Annals of Oncology 2013, 24*:*398-405.

53. Ottewell PD, Wang N, Brown HK, et al.: Zoledronic acid has differential antitumor activity in the pre- and postmenopausal bone microenvironment in vivo. Clin Cancer Res. 2014, 20:2922-2932.

54. Early Breast Cancer Clinical Trials Collaborative Group (EBCTCG) Adjuvant bisphosphonate treatment in early breast cancer: meta-analyses of individual patient data from randomised trials. Lancet 2015; 386(10001):1353-61.

55. Coleman R, Hall A, Albanell J et al. Effect of MAF amplification on treatment outcomes with adjuvant zoledronic acid in early breast cancer: a secondary analysis of the international, open-label, randomised, controlled, phase 3 AZURE (BIG 01/04) trial. Lancet Oncol. 2017; 18, 1543-1552.

56. Pavlovic M, Arnal-Estapé A, Rojo F, et al. Enhanced MAF Oncogene Expression and Breast Cancer Bone Metastasis. J Natl Cancer Inst 2015; 107: djv256.

57. Zuberbuehler M, Parler M, Wheaton J. The transcription factor c-Maf is essential for the commitment of IL-17-producing γδ _T cells. Nature Immunology 2019; 20(1): 73-85

58. P Hadji, RE Coleman, C Wilson, et al. Adjuvant bisphosphonates in early breast cancer: Consensus guidance for clinical practice from a European Panel. Annals of Oncology 2016; 27(3):379-90.

59. Dhesy-Thind S, Fletcher GG, Blanchette PS, et al. Use of Adjuvant Bisphosphonates and Other Bone-Modifying Agents in Breast Cancer: A Cancer Care Ontario and American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol 2017; 35,2062-2081.

60. Gnant M, Pfeiler G, Steger GG, et al. Adjuvant denosumab in postmenopausal patients with hormone receptor-positive breast cancer (ABCSG-18): disease-free survival results from a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol 2019; 20, 339-351.

61. Coleman RE, Finkelstein D, Barrios CH et al. Adjuvant denosumab in early breast cancer: primary results from the international, multicenter, randomized, phase 3, placebo-controlled D-CARE study. *Lancet Oncology,* 2020 Jan;21(1):60-72.

62. Sisay M, Mengistu G, Edessa D The RANK/RANKL/OPG system in tumorigenesis and metastasis of cancer stem cell: potential targets for **anticancer** therapy. Onco Targets Ther. 2017 Jul 27;10:3801-3810

63. Gnant M, Pfeiler G, Dubsky PC, et al.: Adjuvant denosumab in breast cancer (ABCSG-18): a multicentre, randomised, double-blind, placebo-controlled trial. Lancet. 2015, *386:*433-443.

64. Kohno N, Aoqi K, Minami H, et al. Zoledronic acid significantly reduces skeletal complications compared with placebo in Japanese women with bone metastases from breast cancer: a randomized, placebo-controlled trial. J Clin Oncol 2005; 20:3299–3301.

Table 1: Key results from studies with bisphosphonates to prevent skeletal-related events in patients with breast cancer and bone metastases

Drug (comparator)	**% SRE**	**Median time to first SRE**	**Other endpoints**	**Refs**
Clodronate (Placebo)	NE	NE	SMR - 219 vs 305	16
Pamidronate (Placebo)	43% vs 56%	399 vs 213 days	Improved QOL and pain	13
Pamidronate (Placebo)	56% vs 67%	317 vs 210 days	Improved QOL and pain	14
Zoledronate (Placebo)	30% vs 50%	NR vs 364 days	Improved pain	46
Zoledronate (Pamidronate)	43% vs 45%	310 vs 174 days	20% risk reduction for SRE	22, 26
Ibandronate oral (Placebo)	NE	632 vs 454 days	SMPR - 0.99 vs 1.15	19
Ibandronate i.v. (Placebo)	51% vs 62%	354 vs 232 days	SMPR - 1.19 vs 1.48	20
Denosumab (Zoledronate)	NE	NR vs 804 days	23% risk reduction for SRE	27

NE, not evaluable; NR, not reached; QOL, quality of life; SRE, skeletal related event; SMR, skeletal morbidity rate; SMPR, skeletal morbidity period rate

Highlights

Bisphosphonates have transformed the care of breast cancer patients with bone metastases and are firmly established as a key element of standard treatment throughout the course of the disease.

In postmenopausal women with early breast cancer, bisphosphonates reduce bone recurrences by about one quarter and cancer deaths by one sixth.

Due to limited understanding of the underlying biology of metastasis and the limitations of animal model systems, the clinical development of bisphosphonates in oncology has been relatively slow and complex and largely reliant on discoveries and innovation from academic groups rather than “big pharma”.