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REVIEW

Bone antiresorptive agents in the treatment of bone metastases associated with solid tumours or multiple myeloma

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Skeletal lesions contribute substantially to morbidity and mortality in patients with cancer. The disease manifestation course during metastatic bone disease is driven by tumour cells in the bone marrow, which alter the functions of bone-resorbing (osteoclasts) and bone-forming (osteoblasts) cells, promoting skeletal destruction. Successful therapeutic strategies for the treatment of metastatic bone disease include bisphosphonates and denosumab that inhibit osteoclast-mediated bone resorption. Inhibitors of cathepsin K, Src and activin A are under clinical investigation as potential anti-osteolytics. In this review, we describe current knowledge and future directions of antiresorptive therapies that may reduce or prevent destructive bone lesions from solid tumours and multiple myeloma.

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Introduction

Solid tumours (breast, prostate and lung cancer) and multiple myeloma are prone to develop bone diseases that are frequently associated with potentially debilitating or life-limiting skeletal-related events (SREs), such as pathological fractures, nerve compression, hypercalcemia and cancer-induced bone pain.[1] Studies of the biology underlying bone metastasis support the notion that tumour cells residing in the bone marrow alter the functions of bone-resorbing (osteoclasts) and bone-forming (osteoblasts) cells and hijack signals coming from the bone matrix.[1] In multiple myeloma, tumour cells originate in the bone marrow and, either alone or through interactions with the bone marrow stromal cells, also alter bone homoeostasis. Specifically, tumour cells from solid tumours and multiple myeloma secrete factors that stimulate osteoclast activity through the activation of the receptor activator of nuclear factor-κB ligand (RANKL)/RANK pathway, which is the primary mediator of osteoclast-mediated bone resorption.[1,2] In addition, tumour cells depress osteoblast formation, which leads to an imbalance between bone resorption and bone formation, resulting in skeletal destruction.[1,2] As the bone is resorbed, bone-derived growth factors that are stored in the bone matrix are released and stimulate tumour growth.[1] Calcium released from bone mineral also stimulates tumour growth through calcium-sensing receptors expressed by tumour cells.[1] The realisation that in osteolytic lesions an interplay between bone cells and tumour cells exists led to the clinical use of inhibitors of osteoclast-mediated bone resorption, such as bisphosphonates (BPs; clodronate, pamidronate, ibandronate and zoledronate) and the RANKL inhibitor denosumab.[2] These antiresorptive agents (zoledronate and denosumab) are the current standard of care for prevention and reduction in SREs in patients with advanced cancer and skeletal lesions.[2] They have been also studied in randomised trials in the adjuvant setting of early cancer, in order to investigate their ability to either prevent cancer treatment-induced bone loss and/or impede disease recurrence and metastases.[2]

In this review article, we have critically reviewed the pre-clinical and clinical evidence supporting the use of BPs and denosumab in the treatment of patients with solid tumours or multiple myeloma with advanced- or early-stage disease. We also provide an overview of novel antiresorptive agents that might further improve the pharmacologic treatment of skeletal lesions in the future.

Bisphosphonates

Pre-clinical evidence

BPs bind avidly to bone mineral and are ingested by osteoclasts, resulting in inhibition of osteoclast-mediated bone resorption[3]. The second-generation nitrogen-containing

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BPs (N-BPs; for example, zoledronate, ibandronate and pamidronate) have been proven more effective at reducing SREs compared with the first-generation BP compounds (for example, clodronate).[2] BPs act intracellularly. N-BPs specifically interfere with farnesyl pyrophosphate synthase, a key enzyme in the mevalonate pathway.[3] This prevents the biosynthesis of isoprenoids necessary for the prenylation and, hence, membrane localisation and functions of small guanosine triphosphatases that are essential for osteoclast activity and survival.[3] Non-N-BPs cause the intracellular accumulation of a cytotoxic analogue of adenosine triphosphate that induces osteoclast apoptosis.[3]

N-BPs reduce skeletal tumour burden in a variety of mouse models of bone metastasis from solid tumours (breast, prostate, lung, ovarian, bladder and renal cell carcinomas) and multiple myeloma, and this reduction has been attributed primarily to the antiresorptive activity of BPs.[2,3] By inhibiting bone resorption, BPs deprive tumour cells of bone-derived growth factors that are required for tumour outgrowth in the bone marrow.[3] BPs might also alter the retention of calcium-sensing receptor-expressing tumour cells in the bone marrow by inhibiting the release of ionic calcium from bone mineral.[3] Of note, the presence of disseminated tumour cells in the bone marrow and/or circulating tumour cells in the peripheral blood of patients with cancer represents the earliest sign of metastatic disease.[4] Interestingly, the pretreatment of animals with a single, clinically relevant dose of zoledronate 5 days before tumour cell inoculation reduced the number of circulating tumour cells and altered the distribution of disseminated tumour cells to osteoblast-rich areas in the bone.[5] Thus, BPs (by inhibiting bone resorption) might alter disseminated tumour cell survival in the bone marrow. These experimental findings are sustained by clinical studies showing that zoledronate and ibandronate decrease the number of disseminated tumour cells in bone marrow aspirates of patients with early-stage breast cancer.[6–8]

There is experimental evidence suggesting that N-BPs also inhibit the growth of tumours outside the skeleton.[2,3] Indeed, *in vitro*, N-BPs inhibit tumour cell adhesion, migration, invasion and proliferation and induce tumour cell apoptosis, when these compounds are used as single agents or in combination with cytotoxic agents.[3,6] However, high doses of N-BPs have been used in most of *in vivo* studies, and such high doses are incompatible with approved BP-dosing regimens for patients with bone metastatic disease.[2] Nevertheless, N-BPs may exert indirect anti-tumour effects *in vivo*. The bone marrow is a reservoir for endothelial progenitor and proangiogenic $CD11b^+$ myelomonocytic cells, and these bone marrow-derived cells contribute to the vascularisation of primary tumours and metastases.[2,3] Therefore, N-BPs may inhibit tumour-associated angiogenesis by blocking the recruitment of bone marrow-derived endothelial progenitors and myelomonocytic cells to the site of tumours. In addition, zoledronate treatment of tumour-bearing animals results in M2 (anti-inflammatory, proangiogenic) to M1 (anti-tumour) reversion of $CD11b^+$ macrophages, infiltrating mammary tumours *in vivo*.[3] Indeed, BPs bind to small, granular microcalcifications in breast tumours, which are then engulfed by $CD11b^+$ macrophages, explaining the presence of BPs in tumours outside the bone and the inhibitory effect that these agents exert on tumour-associated macrophages.[3,9]

Increased cancer surveillance via activation of γδT cells may represent another potential mechanism through which N-BPs may exhibit anticancer activity.[2,3] Human Vγ9 Vδ2 T cells are a subset of human T cells that exhibits anticancer activity. As a result of the inhibition of FPP synthase, N-BPs induce intracellular accumulation of isopentenyl pyrophosphate in tumour cells *in vitro* and *in vivo*, which is sensed by Vγ9Vδ2 T cells as a tumour phosphoantigen, triggering Vγ9Vδ2 T-cell anti-tumour cytotoxicity.[2,3]

Clinical evidence for BP therapy in patients with advanced disease

Metastatic breast cancer. The effects of BPs (clodronate, pamidronate, ibandronate and zoledronate) on prevention and reduction in SREs associated with bone metastases from breast cancer have been extensively studied (**Table 1**). They all have demonstrated clinical benefits on reduction in skeletal morbidity, the N-BP zoledronate being the most potent agent with a 40% reduction in the risk of developing an SRE, compared with placebo (**Table 1**). In addition, a direct comparison of zoledronate vs pamidronate or zoledronate vs ibandronate in two different large clinical trials showed that zoledronate is preferable to the other agents in reducing the risk of developing SREs (**Table 1**). Overall, the use of BPs to prevent or reduce SREs has resulted in a substantial improvement of the quality of life of patients with breast cancer and bone metastasis.[10] The practice guidelines regarding the use of a BP therapy for breast cancer patients with bone metastasis are pamidronate 90 mg intravenously over no <2 h or zoledronate 4 mg intravenously over no <15 min every 3–4 weeks.[11]

Metastatic prostate cancer. Bone metastases in prostate cancer appeared radiographically dense reflecting an increased bone formation activity. Nevertheless, this new bone is mainly sclerotic woven bone with poor mechanical properties and prostate cancer patients with bone metastases experience SREs. In addition, the high bone turnover, as assessed by bone resorption markers, justifies the use of antiresorptive agents in the treatment of prostate cancer bone metastases.[2]

After a 4.9-year median follow-up, clodronate treatment of patients with castration-sensitive prostate cancer and bone metastases was associated with a nonsignificant trend toward improvement of SREs (hazard ratio; $HR = 0.79$; $P = 0.066$) and overall survival ($HR = 0.8$; $P = 0.082$) (**Table 1**). Notably, a subsequent study with a 11.5-year median follow-up revealed an improved overall survival in the clodronate group (**Table 1**). In contrast, zoledronate treatment of men with castration-sensitive prostate cancer and bone metastases did not reduce the risk for SREs and did not improve overall survival compared with the placebo group (**Table 1**).

In men with castration-resistant prostate cancer and symptomatic bone metastases, pamidronate failed to reduce SREs, whereas zoledronate substantially altered the progression of metastatic bone disease as noted by an increased time to first SRE and a 36% reduction in the risk of subsequent SREs (**Table 1**). No overall survival benefit was, however, observed. On the basis of these results, zoledronate has received regulatory approval for patients with prostate cancer and bone metastases who have progressed despite hormonal therapy.

Table 1 Effects of a bisphosphonate therapy on skeletal-related events associated with bone metastases in patients with solid tumours or advanced multiple myeloma

Bisphosphonate	N	*Results*	*Investigator (ref.)*
Metastatic breast cancer			
clodronate (1600 mg po, daily) vs placebo	173	Decreased SREs (218 vs 304/100 patient-years; $P<0.001$)	Paterson *et al.*[38]
pamidronate (45 mg iv, q 3 weeks) vs placebo	295	Increased time to progression (249 vs 168 days; $P=0.02$)	Conte *et al.*[39]
pamidronate (90 mg iv, q 4 weeks for 12 cycles) vs placebo	380	Increased time to first SRE (13.1 vs 7 months; $P=0.005$)	Hortobagyi *et al.*[40]
pamidronate (90 mg iv, q 4 weeks for 24 cycles) vs placebo	371	Decreased proportion of patients with SREs ($P=0.027$)	Theriault *et al.*[41]
pamidronate (60 mg iv, q 4 weeks) vs placebo	404	Increased time to progression (14 vs 9 months, $P<0.01$)	Hultborn *et al.*[42]
pamidronate (90 mg iv, q 3-4 weeks) vs zoledronate (4/8 mg iv, q 3–4 weeks) for 2 years	1009	compared with pamidronate, 4- mg zoledronate reduced the risk of SREs by an additional 16% ($P=0.03$)	Rosen *et al.*[43]
ibandronate (2/6 mg iv, q 4 weeks for 2 years) vs placebo	466	6- mg dose decreased SREs ($P<0.004$); 2 mg ineffective	Body *et al.*[44]
ibandronate (50 mg po, daily for 96 weeks) vs placebo	564	Decreased SREs (HR = 0.63, 95% CI = 0.48–0.79; $P<0.0001$)	Body *et al.*[45]
ibandronate (50 mg po, daily) vs zoledronate (4 mg iv, q 3-4 weeks) for 96 weeks	1326	zoledronate is preferable to ibandronate in preventing SREs	Barrett-Lee *et al.*[46]
zoledronate (4 mg iv, q 4 weeks for 1 year) vs placebo	228	41% reduction in the risk of SREs ($P=0.019$)	Kohno *et al.*[47]
Metastatic prostate cancer			
clodronate (2080 mg po, daily for 3 years) vs placebo in castration-sensitive prostate cancer (MRC PR 05 study)	278	After a 11.5-year median follow-up, improved OS for the clodronate group (HR = 0.77, 95% CI 0.6–0.98; $P=0.032$)	Dearnaley *et al.*[48,49]
pamidronate (90 mg iv, q 3 weeks for 27 weeks) vs placebo in castration-resistant prostate cancer	378	no statistically significant benefit in the pamidronate group	Small *et al.*[50]
zoledronate (4 mg iv, q 3 weeks for 15 months) vs placebo in castration-resistant prostate cancer	643	Increased time to first SRE (488 days vs 321 days; $P=0.009$). 36% reduction in the risk of SREs ($P=0.002$)	Saad *et al.*[51]
zoledronate (4 mg iv, q 4 weeks) vs placebo in castration-sensitive prostate cancer (CALGB 90202 study)	645	no improvement in OS (HR = 0.88; $P=0.29$) and no prevention of SREs (HR = 0.97; $P=0.39$)	Smith *et al.*[52]
Other metastatic cancers			
zoledronate (4 mg iv, q 3 weeks) vs placebo in stage IV NSCLC	144	Increased time to progression (265 days vs 150 days; $P<0.001$) and OS (578 days vs 384 days; $P<0.01$)	Zarogoulidis *et al.*[12]
zoledronate (4 mg iv, q 3 weeks for 21 months) vs placebo in NSCLC and other solid tumours	773	Increased time to first SRE (236 days vs 155 days; $P=0.009$). 31% reduction in the risk of subsequent SREs ($P=0.003$)	Rosen *et al.*[53]
zoledronate (4 mg iv, q 3 weeks for 9 months) vs placebo in renal cell carcinoma	74	61% reduction in the risk of SREs ($P=0.008$)	Lipton *et al.*[54]
Zoledronate (4 mg iv, q 4 weeks for 6 months) vs placebo in bladder cancer	40	Compared with placebo, zoledronate prolonged the median time to first SRE (16 vs 8 weeks) and increased the 1-year survival rate (36.3 vs 0%)	Zaghloul *et al.*[55]
Advanced multiple myeloma			
clodronate (1600 mg po, daily) vs placebo	350	12% improvement in RFS ($P=0.026$)	Lahtinen *et al.*[56]
clodronate (1600 mg po, daily) vs placebo	535	Decreased proportion of patients with SREs. No benefit in OS. However, among patients without vertebral fractures at study entry ($n=153$, *post hoc* analysis), there was an increased OS ($P=0.006$)	McCloskey *et al.*[57,58]
pamidronate (90 mg iv, q 4 weeks for 21 cycles) vs placebo	392	Decreased proportion of patients with SREs ($P=0.015$)	Berenson *et al.*[59]
zoledronate (4 mg iv, q 4 weeks) vs placebo for 2 years	308	After a 5.8-year median follow-up, zoledronate improved RFS ($P<0.001$) and OS ($P<0.001$)	Avilès *et al.*[60]

Abbreviations: CI, confidence interval; HR, hazard ratio; iv, intravenous; NSCLC, non-small cell lung carcinoma; OS, overall survival; po, *per os*; RFS, relapse-free survival; SRE, skeletal-related event.

Other metastatic cancers. Patients with documented bone metastases secondary to lung carcinoma ($n=436$), mainly non-small cell lung cancer (NSCLC), and to solid tumours other than breast or prostate who were treated with zoledronate experienced fewer SREs and a significantly reduced annual incidence rate of skeletal complications (1.74 events per year vs 2.71; **Table 1**). Furthermore, multiple-event analysis revealed that patients treated with zoledronate had a 31% reduced risk of developing skeletal complications, compared with patients who received placebo (**Table 1**). More recent data from a prospectively designed trial on patients with stage IV NSCLC and symptomatic bone metastases confirmed the cancer-related benefits of zoledronate.[12] Notably, compared with placebo, zoledronate not only increased the time to progression but also improved overall survival (**Table 1**). Moreover, longer duration of zoledronate therapy correlated with both prolonged overall survival ($P<0.01$) and the time to progression ($P<0.01$), suggesting that these effects were mediated by the BP.[12]

Data on the effects of BPs in patients with other types of cancer at the metastatic stage are limited. Data from a prospective, placebo-controlled trial in patients with bladder cancer and bone metastasis ($n=40$) showed that, compared with placebo, zoledronate prolonged the time to first SRE and improved the 1-year survival rate (**Table 1**). Similarly, zoledronate reduced by 61% the risk of subsequent SREs in patients with bone metastases from renal cell carcinoma ($n=74$), compared with placebo (**Table 1**). However, data from such small trials need to be interpreted with caution. Larger studies that explore the cancer-related benefit of zoledronate in patients with advanced renal cell and bladder cancers are needed.

Advanced multiple myeloma. BPs effectively reduce SREs in multiple myeloma patients (**Table 1**). Clinical data have confirmed pre-clinical observations that BPs may have anti-myeloma activity. It is important to mention that a survival advantage was shown in very different patient subpopulations:

those with no fractures at baseline in clodronate studies, those who received second-line therapy in pamidronate studies or finally those with high bone resorption or bone disease at baseline in zoledronate studies (**Table 1**). Currently, zoledronate and pamidronate intravenously are the BPs used in multiple myeloma patients with bone disease.[13]

Clinical evidence for BP therapy in patients with early disease

Breast cancer. The earliest evidence that BPs may prevent bone metastasis in early breast cancer derives from the data of two randomised, prospective trials with clodronate (**Table 2**). These trials indicated that a 2-year treatment with clodronate not only improved disease-free survival but also prolonged overall survival (**Table 2**). A third trial with clodronate (Saarto's study) did not confirm these data (**Table 2**). Instead, it suggested an adverse effect of clodronate with an increase in extraosseous metastases (**Table 2**). However, the population of the Saarto's study was not well balanced between the clodronate and the placebo groups with respect to the progesterone receptor status (there were more patients with progesterone-negative breast cancer in the clodronate group; $P = 0.03$), and the number of patients with distant metastases at the time of randomisation was higher in the clodronate group than in the placebo group (9/149 vs 6/150, respectively). This may have influenced the study outcome. Importantly, a fourth large phase-III trial (NSABP B-34 trial; $n = 3323$) provided evidence that adjuvant treatment with clodronate improved disease-free survival (**Table 2**). This benefit was, however, restricted to women >50 years (**Table 2**). Overall, these results spurred further clinical evaluations to examine the potential of more potent BPs to prevent relapse in breast cancer.

Three large phase-III, prospective clinical trials were conducted with zoledronate during adjuvant therapy with endocrine therapy, chemotherapy or aromatase inhibitors (ABCSG-12, ZO-FAST and AZURE; **Table 2**). The data from these clinical trials suggested that zoledronate may demonstrate anticancer activity in patients with ER-positive breast cancer who had low levels of reproductive hormones at study entry, achieved either through natural menopause or ovarian suppression therapy (**Table 2**). Using adjuvant ibandronate in early breast cancer, no differences in relapse-free survival and overall survival between the placebo and the ibandronate groups were seen (GAIN trial; **Table 2**). However, there was again a trend in favour of ibandronate in postmenopausal women. Similarly, a benefit was reported with adjuvant clodronate in women over the age of 50 years (NSABP B-34 trial; **Table 2**). The mechanisms behind improved relapse-free survival and overall survival of these patients in a low oestrogen environment who received zoledronate (ibandronate or clodronate) are unknown.

Of note, the Early Breast Cancer Trials Collaborative Group (EBCTCG) has conducted a meta-analysis of individual patient data from 18 766 women involved in 26 randomised trials of adjuvant BPs for early breast cancer.[14] A total of 3453 and 2, 106 breast cancer recurrences and deaths were reported, respectively. For the entire population, BPs reduced the number of patients with first distant recurrence in the bone (relative risk; RR = 0.83; 95% confidence interval; (CI) 0.73–0.94, $P = 0.004$) but had little effect on other clinical outcomes. However, in postmenopausal women ($n = 11\,767$), BPs not only improved the time to first distant recurrence in bone (RR = 0.72; 95% CI 0.74–0.92, $P \leqslant 0.001$) but also overall breast cancer recurrence (RR = 0.86; 95% CI 0.78–0.94, $P = 0.001$), distant recurrence at any site (RR = 0.82; 95% CI 0.73–0.93, $P = 0.001$) and breast cancer mortality (RR = 0.82; 95% CI 0.73–0.93, $P = 0.002$). By contrast, BPs did not modify disease outcomes in premenopausal women.

Risk reductions in postmenopausal women treated with BPs were similar irrespective of the type of BP (amino vs non-amino), with the outcomes in the clodronate trials at least as good as those achieved with the more potent aminoBPs. Thus, the benefit of using adjuvant BPs in postmenopausal women with early breast cancer is most likely due to the antiresorptive properties of these agents.

Prostate cancer. Zoledronate has long-term benefits in patients with castration-resistant prostate cancer and bone metastases (**Table 1**). The use of zoledronate in an adjuvant setting (ZEUS trial), after a 4-year follow-up, did not, however, provide a benefit on disease-free survival in patients with high-risk localised prostate cancer, regardless whether these men received or did not receive androgen-deprivation therapy (**Table 2**). In addition, adjuvant clodronate treatment failed to prevent bone metastasis in patients with castration-sensitive prostate cancer (**Table 2**). Up to now, only the RADAR trial showed a benefit from using zoledronate in men with castration-sensitive prostate cancer, especially in patients with tumours with Gleason score 8–10 (**Table 2**). It is proposed that high-grade prostate cancers might be more vulnerable to zoledronate because of their greater dependence on the mevalonate pathway.[15] Results of the STAMPEDE trial (**Table 2**), in which the value of zoledronate and other treatment options was tested in castration-sensitive prostate cancer, are awaited with interest.

Multiple myeloma. On the basis of promising results in the metastatic setting (**Table 1**), a large phase-III trial, the MRC Myeloma IX trial, was conducted to evaluate the effects of zoledronate vs clodronate in 1960 newly diagnosed myeloma patients (**Table 2**). After 5.9 years of follow-up, patients treated with zoledronate had a better chance of survival with an improvement in median overall survival of 6 months compared with patients treated with clodronate (52 vs 46 months; HR of death = 0.86; 95% CI, 0.77–0.97; $P = 0.01$).[16] Median progression-free survival was also significantly longer with zoledronate compared with clodronate (19 vs 18 months; HR = 0.89; 95% CI, 0.80–0.98; $P = 0.02$; **Table 2**).[16] Notably, the survival benefit with zoledronate, observed within the first 6 months, remained statistically significant after adjustment for SREs and thus was consistent with clinically meaningful anti-myeloma activity.[16] The results of this study support the early use of zoledronate rather than clodronate in patients with newly diagnosed multiple myeloma for the prevention of SREs, irrespective of bone disease status at baseline.[13] In this respect, recommendations of the International Myeloma Working Group are to use intravenous zoledronate every 3–4 weeks during initial therapy. BPs zoledronate or pamidronate should be then continued in patients with active disease and should be resumed after disease relapse, if discontinued in patients achieving complete or very good partial response.[13]

Table 2 Effects of a bisphosphonate therapy on prevention of metastases in patients with early cancer (solid tumours or multiple myeloma)

Bisphosphonate	N	*Results*	*Investigator (ref.)*
Breast cancer			
clodronate (1600 mg po, daily for 2 years) vs placebo in ER-positive and ER-negative breast cancer patients with DTCs in the bone marrow	302	Improvement of RFS ($P = 0.003$) and OS ($P = 0.0001$). After a 8.5-year median follow-up, no more reduction in RFS but still a benefit in OS ($P = 0.04$)	Diel *et al.*[61,62]
clodronate (1600 mg po, daily for 2 years) vs placebo in ER-positive and ER-negative breast cancer	1069	After a 5.6-year median follow-up, clodronate reduced the risk of bone metastasis by 31% ($P = 0.043$) and improved OS (HR = 0.76; $P = 0.048$)	Powles *et al.*[63,64]
clodronate (1600 mg po, daily for 3 years) vs placebo in node-positive, ER-positive and ER-negative breast cancer	299	After a 10-year follow-up, decreased RFS in the clodronate group ($P = 0.01$). Of note, at baseline, there were more progesterone-negative patients in the clodronate group ($P = 0.03$)	Saarto *et al.*[65,66]
clodronate (1600 mg po, daily for 3 years) vs placebo in ER-positive and ER-negative breast cancer (NSABP B-34 study)	3323	No improvement in OS and RFS. In women with > 50 years on study entry, there was a 25% reduction in RFS ($P = 0.045$)	Paterson *et al.*[67]
ibandronate (50 mg po, daily for 2 years) vs observation in ER-positive and ER-negative breast cancer (GAIN study)	2015	no improvement of RFS or OS	von Minckwitz *et al.*[68]
zoledronate (4 mg iv, q 6 months for 5 years) in premenauposal ER-positive breast cancer (ABCSG-12 study)	1803	After a 7.9-year median follow-up, reduced disease progression by 23% ($P = 0.04$) but did not affect risk of death.	Gnant *et al.*[26,69,70]
immediate zoledronate (4 mg iv, q 6 months for 5 years) or delayed zoledronate (initiated for fracture or low bone mineral density) in postmenopausal women with ER-positive breast cancer (Z-FAST study)	602	no statistically significant difference in RFS between the immediate- and delayed-zoledronate groups	Brufsky *et al.*[71,72]
immediate zoledronate (4 mg iv, q 6 months for 5 years) or delayed zoledronate (initiated for fracture or low bone mineral density) in postmenopausal women with ER-positive breast cancer (ZO-FAST study)	1065	immediate zoledronate decreased RFS by 34% ($P = 0.037$) vs delayed zoledronate	EBCTCG[14]
zoledronate (4 mg iv q 3–4 weeks × 6, 4 mg iv q 3 months x 8, 4 mg iv q 6 months × 5) in ER-positive and –negative breast cancer (AZURE study)	3360	After a 7-year median follow-up, no improvement in OS and RFS. However, in women > 5 years post menopause before study entry, there was a benefit in RFS (HR = 0.75; $P = 0.02$) and OS (HR = 0.81; $P = 0.04$)	Coleman *et al.*[73,74]
Prostate cancer			
clodronate (2080 mg po, daily for 5 years) vs placebo in castration-sensitive prostate cancer (MRC PR04 study)	508	After a 12-year median follow-up, no improvement in OS (HR = 1.12; $P = 0.94$) and no prevention of bone metastasis (HR = 1.22)	Mason *et al.*[75] Dearnaley *et al.*[76]
zoledronate (4 mg iv, q 3 months for 18 months) in castration-sensitive prostate cancer (RADAR study)	1071	For men with Gleason score 8–10, zoledronate + androgen-deprivation therapy commencing 5 months before radiotherapy decreased the risk of distant progression by more than 40%	Denham *et al.*[15]
zoledronate (4 mg iv, q 3 months for 4 years) in high-risk localised prostate cancer (ZEUS study)	1393	Ineffective in the prevention bone metastasis	Wirth *et al.*[77]
Androgen suppression-based therapy alone or combined with zoledronate, docetaxel, prednisolone, celecoxib, abiraterone, enzalutamide and/or radiotherapy in treating patients with locally advanced or metastatic prostate cancer (STAMPEDE study)	> 8000	Accrual ongoing	ClinicalTrials.gov Identifier: NCT00268476
Multiple myeloma			
Clodronate (1600 mg po, daily, vs placebo) (MRC Myeloma VI study)	535	After a 8.6-year median follow-up, increased OS ($P = 0.006$) in patients without vertebral fracture at study entry ($n = 153$; *post hoc* analysis)	McCloskey *et al.*[57,58]
zoledronate (4 mg iv, q 3–4 weeks) vs clodronate (1600 mg po, daily) (MRC Myeloma IX study)	1960	After a 5.9-year median follow-up, zoledronate reduced mortality by 14% (HR = 0.86; $P = 0.01$) and decreased incidence of SREs by 11% (HR = 0.89; $P = 0.02$)	Morgan *et al.*[16,78,79]

Abbreviations: CI, confidence interval; DTC, disseminated tumour cell; HR, hazard ratio; iv, intravenous; OS, overall survival; po, *per os*; RFS, relapse-free survival; SRE, skeletal-related event.

Denosumab

Pre-clinical evidence

Osteoclast-mediated bone resorption, governed by RANK/RANKL, has a critical role in the expansion of tumour cells in the bone.[1] Osteoprotegerin (OPG), a decoy receptor for RANKL, inhibits bone resorption by counterbalancing RANKL activity.[1] As a consequence, the treatment of animals with Fc-engineered OPG-Fc fusion protein is capable of inhibiting bone destruction and reducing skeletal tumour burden in bone metastasis models of breast, prostate, lung, colon and renal cancer and in animal models of multiple myeloma.[17,18] In addition, OPG-Fc provides a greater benefit to reduce skeletal

Table 3 Effects of a therapy with anti-RANKL antibody denosumab on skeletal-related events (SREs) associated with bone metastases in patients with solid tumours or advanced multiple myeloma

Study population	*N*	*Results*	*Investigator (ref.)*
Metastatic breast cancer			
Denosumab (120 mg sc) and placebo iv vs zoledronate (4 mg iv) and placebo sc, q 4 weeks	2046	Denosumab was superior to zoledronate in delaying the time to first on-study SRE (HR = 0.82; $P = 0.01$)	Stopeck *et al.*[80]
Metastatic prostate cancer			
Denosumab (120 mg sc) and placebo iv vs zoledronate (4 mg iv) and placebo sc, q 4 weeks, in patients with CRPC	1901	Denosumab was superior to zoledronate in delaying the time to first on-study SRE (HR = 0.82; $P = 0.008$)	Fizazi *et al.*[81]
Other metastatic cancers			
Denosumab (120 mg sc) and placebo iv vs zoledronate (4 mg iv) and placebo sc, q 4 weeks, in patients with cancer other than breast and prostate cancer or multiple myeloma	1776	Denosumab was noninferior to zoledronate in delaying the time to first on-study SRE (HR = 0.84, $P = 0.0007$). There was a trend to superiority ($P = 0.06$)	Henry *et al.*[25]
Denosumab (120 mg sc) and placebo iv vs zoledronate (4 mg iv) and placebo sc, q 4 weeks, in patients with lung cancer (exploratory analysis in patients who participated in the Henry's study)	811	Denosumab improved OS compared with zoledronate with any lung cancer (8.9 vs 7.7 months; HR = 0.8; $P = 0.01$) and with NSCLC (9.5 vs 8 months; HR = 0.78; $P = 0.01$)	Scagliotti *et al.*[82]
Advanced multiple myeloma			
A randomised, double-blind study of denosumab (120 mg sc, q 4 weeks) compared with zoledronate (4 mg iv, q 4 weeks) in the treatment of bone disease in subjects with newly diagnosed multiple myeloma	1520	Accrual ongoing. Primary outcome: time to the first on-study SRE (non-inferiority test)	ClinicalTrials.gov Identifier: NCT01345019

Abbreviations: CRCP, castration-resistant prostate cancer; HR, hazard ratio; iv, intravenous; NSCLC, non-small cell lung carcinoma; OS, overall survival; sc, subcutaneous; SRE, skeletal-related event.

tumour growth of MDA-MB-231 breast cancer cells in animals when compared with that observed with the BP zoledronate.[18] This reduction in tumour burden is likely related to inhibition of osteoclast-mediated bone resorption because OPG-Fc does not affect tumour growth in soft tissues.[18,19]

The RANK/RANKL/OPG triad is not only expressed by bone cells but also by a number of different human tumour cell lines. For example, RANKL stimulates the migration and invasion of RANK-expressing human breast, prostate, lung and renal cancer cells and melanoma cells *in vitro*.[18] Tumour-derived OPG promotes the survival of prostate cancer cells.[18] *In vivo*, overexpression of RANK in human MDA-MB-436 and MDA-MB-231 breast cancer cells promotes experimental lung and bone metastasis formation, respectively, compared with that observed with their respective parental cell lines.[18] There is also evidence that RANK-Fc treatment substantially decreased lung metastasis formation in animals spontaneously developing mammary tumours, whereas it did not change the median time to mammary tumour formation.[18]

An association of RANK/RANKL/OPG expression levels in primary tumours with poor clinical outcome of patients has been reported.[18] In primary breast cancer, a high expression of RANK (both at the mRNA and protein levels) was significantly associated with a shorter bone metastasis-free survival and a poorer overall survival.[18,19] Only 30% of infiltrating primary breast carcinomas express RANKL.[18] High expression levels of RANK/RANKL in primary prostate and renal cell carcinomas and NSCLC were associated with a poor clinical outcomes.[18,20,21] In addition, high OPG levels in prostate cancer were associated with more advanced metastatic tumours.[20] In contrast, low OPG levels in renal cell carcinomas were associated with a shorter bone metastasis-free survival.[18] Overall, these observations[18–21] provided a rationale for the use of denosumab in an adjuvant setting.

Denosumab is a fully human monoclonal antibody with high affinity and specificity for RANKL, and it inhibits the RANKL–RANK interaction.[18] In this respect, this agent inhibits osteoclast differentiation and the resorptive activity of mature osteoclasts. Denosumab has been developed later than BPs and was compared head-to-head with zoledronate in clinical trials. The pharmacokinetic and pharmacodynamic properties of denosumab and zoledronate are quite different. The effect of denosumab on inhibition of bone resorption is reversible when the treatment is discontinued. BPs, including zoledronate, remain in the bone for a long period of time, suggesting that after drug discontinuation BPs embedded in the bone may still be active for the suppression of bone turnover.[22]

Clinical evidence for denosumab therapy in patients with advanced disease

Metastatic breast cancer. The effects of denosumab and zoledronate have been compared in a large phase-III, double-blind study, most of the patients being hormone receptor positive (72%) (**Table 3**). This study demonstrated the superiority of denosumab to zoledronate in delaying the first on-study SRE (HR = 0.82, $P = 0.01$) and the time of subsequent SREs (HR = 0.77; $P = 0.001$). Reduction in bone turnover biomarkers was greater with denosumab. Overall survival was the same between the denosumab and the zoledronate groups. The practice guideline regarding the use of denosumab for breast cancer patients with bone metastasis is 120 mg subcutaneously every 4 weeks.[9]

Metastatic prostate cancer. The effects of denosumab and zoledronate have been compared in a large phase-III, double-blind study, enroling patients with castration-resistant prostate cancer (**Table 3**). Initially planned as a non-inferiority trial, results demonstrated the superiority of denosumab to delay the time to

Table 4 Effects of a therapy with anti-RANKL antibody denosumab on prevention of metastases in patients with early cancer

Study population	*N*	*Results/primary endpoint*	*Investigator (ref.)*
Breast cancer			
Study of denosumab (120 mg sc, q 4 w × 6, 120 mg sc, q 3 months × 18) vs placebo, as adjuvant treatment for women with high-risk early breast cancer receiving neoadjuvant or adjuvant therapy (D-CARE study)	4509	Accrual ongoing. Primary outcome: bone metastasis-free survival	ClinicalTrials.gov Identifier: NCT01077154
Study to determine treatment effects of denosumab (60 mg sc, q 6 months) vs placebo in patients with breast cancer receiving aromatase inhibitor therapy (ABCSG-18 study)	3420	Denosumab delayed the time to the first clinical fracture, compared with placebo (HR = 0.5; $P < 0.0001$).	Gnant *et al.*[26]
Prostate cancer			
Denosumab (120 mg sc, q 4 weeks) vs placebo in non metastatic CRPC with PSA ⩾ 8 microg/ml or PSA doubling time ⩽ 10 months	1432	Increased bone metastasis-free survival (29.5 vs 25.2 months; HR = 0.85; $P = 0.028$). OS did not differ between groups	Smith *et al.*[83]

Abbreviations: CRPC, castration-resistant prostate cancer; HR, hazard ratio; iv, intravenous; OS, overall survival; PSA, prostate-specific antigen; sc, subcutaneously; SRE, skeletal-related event.

first SRE (median 20.7 months vs 17.1 months; HR = 0.82; $P = 0.008$) and the time to subsequent SREs (HR = 0.82; $P = 0.008$). Between-group divergence started as early as 3 months after treatment initiation. This prevention was observed in both symptomatic and asymptomatic SREs.[23] No benefit on overall survival or disease-free progression was observed. On the basis of these results, denosumab has received regulatory approval to reduce SREs in prostate cancer with bone metastases.[24] The approved dose is 120 mg subcutaneously every 4 weeks. It should be, however, restricted to castration-resistant prostate cancer, as data in metastatic, castrate-sensitive prostate cancer are lacking.[24]

Metastatic lung cancer. The effects of denosumab and zoledronate have been compared in a large phase-III, double-blind study, enroling patients with bone metastases in the setting of a solid tumour (excluding breast or prostate cancer) or with multiple myeloma (**Table 3**). The leading subpopulations comprised patients with NSCLC (40%), SCLC (9%), renal cell carcinomas (6%) and multiple myeloma (10%). The trial met its primary end point of demonstrating significant non-inferiority of denosumab to zoledronate for the time to first SRE (20.6 months vs 16.3 months; HR = 0.84; $P = 0.0007$). There was a trend to superiority in favour of denosumab ($P = 0.06$) (**Table 3**). No benefit on overall survival was observed.

A *post hoc* analysis examining patients with NSCLC who participated in the phase-III trial revealed that the effect of denosumab on the time to first on-study SRE did not differ from that observed with zoledronate (HR = 0.84; $P = 0.2$), whereas there was a benefit in overall survival (HR = 0.79 (0.65–0.95)).[25] To further explore overall survival in patients with NSCLC, an exploratory analysis was conducted (**Table 3**). The results confirmed the overall survival benefit in favour of denosumab (8.9 months vs 7.7 months; HR = 0.8; $P = 0.01$; **Table 3**). Thus, compared with zoledronate, denosumab in NSCLC demonstrated non-inferiority for SREs and superiority for overall survival, leading to its routine use by physicians in clinical practice.

Advanced multiple myeloma. Denosumab has not been extensively studied in multiple myeloma. Results of the phase-III study that included approximately 180 patients with multiple myeloma showed that, although denosumab was comparable to zoledronic acid in delaying occurrence of SREs (HR = 1.03; $P = 0.89$), the overall survival was inferior (HR = 2.26; 95% CI 1.13 to 4.5).[25] This was mainly due to the lack of stratification regarding different anti-myeloma therapies between the denosumab and the zoledronate groups. Therefore, a larger phase-III study (ClinicalTrials.gov identifier NCT01345019) focusing only on multiple myeloma is ongoing.

Clinical evidence for denosumab therapy in patients with early disease

Breast cancer. The Austrian Breast and Colorectal Cancer Study Group Trial-18 (ABCSG-18) compared denosumab treatment (60 mg) with placebo, subcutaneously every 6 months, in 3420 postmenopausal women receiving adjuvant aromatase inhibitor therapy (**Table 4**). Results of this prospective study showed that, compared with the placebo group, patients in the denosumab group had a significantly delayed time to first clinical fracture (HR = 0.50; $P < 0.0001$).[26] For example, at 36 months after randomisation, 5% of the patients in the denosumab group had experienced a fracture, compared with 9.6% in the placebo group.[26] In addition, the incidence of adverse events did not differ between patients who received denosumab or placebo.[26] Thus, denosumab is clearly an effective treatment to prevent fracture in breast cancer patients with a modest risk of disease recurrence.

Another large phase-III trial, which is in progress, is the placebo-controlled study of denosumab treatment (D-CARE study) in 4509 women with high-risk early breast cancer receiving neoadjuvant or adjuvant therapy (**Table 4**). The results of this trial will tell us whether or not denosumab prevents disease recurrence and provides survival benefit.

Prostate cancer. The effects of denosumab (120 mg subcutaneously, q 4 weeks) have been studied in men with nonmetastatic castration-resistant prostate cancer who were considered at high risk of bone metastasis based on the prostate-specific antigen level and/or prostate-specific antigen doubling time (**Table 4**). Denosumab increased bone

Table 5 Novel antiresorptive agents in clinical development

Target	*Compound*	*Cancer type*	*Stage*	*Description/comment*	*Investigator (ref.)*
Cathepsin K	Odanacatib	Breast	Phase II	Safety and efficacy in comparison with ZOL.	Jensen *et al.*[84]
Src	Dasatinib	Prostate	Phase III	Dasatinib + docetaxel vs placebo + docetaxel in men with CRPC (READY trial). No improvement in OS and time to first SRE.	Araujo *et al.*[85]
	Saracatinib	Breast/oprostate	Phase II	Safety and efficacy in comparison with ZOL.	ClinicalTrials.gov identifier NCT00558272
	Bosutinib	Breast	Phase II	Bosutinib prolongs PFS in chemotherapy-pretreated patients. No effect on bone turnover markers.	Campone *et al.*[86]
mTOR	Everolimus	Breast	Approved	Everolimus + exemestane vs placebo + exemestane in metastatic ER-positif breast cancer (BOLERO-2 trial). Reduction in bone turnover markers and improvement of PFS in bone in the everolimus arm.	Gnant *et al.*[30]
		RCC	Phase II	Everolimus vs everolimus + ZOL in RCC patients with $\geq$1 bone metastasis (RAZOR trial). Time to first SRE was 9.6 months on everolimus plus ZOL vs 5.2 months on everolimus ($P = 0.03$).	Broom *et al.*[87]
Activin A	Sotatercept	Myeloma	Phase IIa	Safety and tolerability in relapsed multiple myeloma patients. In patients without bisphosphonate use, anabolic improvements compared with placebo.	Abdulkadyrov *et al.*[88]

Abbreviations: CRPC, castration-resistant prostate cancer; ER, oestrogen receptor; mTOR, mammalian target of rapamycin; OS, overall survival; PFS, progression-free survival; RCC, renal cell carcinoma; SRE,skeletal-related event; Src, proto-oncogene tyrosine-protein kinase; ZOL, zoledronate.

metastasis-free survival by a median of 4.2 months, compared with placebo (**Table 4**). Denosumab treatment also significantly delayed both the time to first bone metastasis and the time to first symptomatic bone metastasis. These effects, however, did not translate into any improvement in the overall survival.

Novel antiresorptive agents

Cathepsin K inhibitors

Cathepsin K is a lysosomal cysteine protease highly expressed in osteoclasts, which degrades collagen during bone resorption.[27] There is pre-clinical evidence that cathepsin K inhibitors (AFG-495, L-235) reduce bone destruction and skeletal tumour burden in animal models of breast cancer bone metastasis.[27,28] A phase-II trial in women with breast cancer and bone metastases shows that the cathepsin K inhibitor odanacatib (which is structurally related to L-235) reduced bone resorption markers after 4 weeks of treatment (**Table 5**).[27] Cathepsin K inhibitors might therefore represent a novel therapy for treatment of metastatic breast cancer.

Src inhibitors

Proto-oncogene tyrosine-protein kinase Src belongs to a family of nonreceptor tyrosine kinases that are activated in response to RANKL/RANK interaction in osteoclasts.[27] The central role played by Src in osteoclast function is exemplified by the observation that Src-null mice inoculated with tumour cells are protected from tumour-associated bone destruction because Src-defective osteoclasts do not resorb bone.[27] Pre-clinical studies also showed that Src inhibitors (CGP76030, AP23451 and dasatinib) successfully inhibit breast cancer cell invasion, growth and bone metastasis formation in animals.[27] Currently, three Src inhibitors (dasatinib, saracatinib and bosutinib) are undergoing clinical studies in patients with cancer and (bone) metastasis (**Table 5**). However, clinical results obtained with these Src inhibitors in metastatic bone disease associated with breast cancer are rather limited and those obtained in metastatic castration-resistant prostate cancer are negative (**Table 5**). Src blockade may result in the activation of compensatory signalling pathways, probably explaining disappointing results that are obtained in the clinic.

mTOR inhibitors

The frequent activation of the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT)/ mammalian target of rapamycin (mTOR) pathway in cancer has made it a much desired target for pharmacologic intervention. In the bone, RANKL and M-CSF promote osteoclast survival by signalling through mTOR.[29] Rapamycin, a mTOR inhibitor, induces osteoclast apoptosis and suppresses bone resorption *in vitro*.[29] Rapamycin also inhibits osteolysis and improves survival in a model of breast cancer bone metastasis.[29] The rapamycin analogue everolimus is under clinical investigation in breast and renal cell carcinoma (**Table 5**). Everolimus combined with aromatase inhibitor exemestane improved progression-free survival in post-menopausal women with hormone receptor-positive breast cancer progressing on prior nonsteroidal aromatase inhibitor therapy (BOLERO-2 trial).[30] Moreover, exploratory analyses from BOLERO-2 have shown that everolimus in combination with exemestane decreased the incidence rate of progressive disease in the bone (8.1% vs 15% in the combination arm and exemestane-only arm, respectively), regardless of BP use and baseline bone metastases (**Table 5**). The bone-sparing effect of everolimus in metastatic breast cancer clearly merits further investigation in an adjuvant setting.

Activin A inhibitor

Activin A, a member of the transforming growth factor-β (TGF-β) superfamily of growth factors, binds to activin type IIA or type IIB receptors, which, in turn, induces the recruitment and phosphorylation of an activin type I receptor B and the subsequent phosphorylation of Smad2 and Smad3 intracellular signalling proteins.[27] Tumour-secreted activin A acts as a stimulator of bone degradation, inhibiting osteoblast differentiation and stimulating osteoclast differentiation in animal models of myeloma and breast cancer.[27] Circulating levels of activin A in the serum of breast or prostate cancer patients with bone metastases are significantly higher compared with those

of patients without bone metastases.[27] On the same note, elevated circulating levels of activin A in patients with advanced multiple myeloma correlate with extensive bone involvement and poor survival.[31] The effects of a soluble chimeric protein composed of the extracellular domain of activin type II receptor A fused to human immunoglobulin G Fc receptor (sotatercept, formerly called ACE-011) have been investigated in newly diagnosed and relapsed multiple myeloma patients (**Table 5**). In multiple myeloma patients without BP use, anabolic improvements in bone mineral density and in bone formation were observed with sotatercept, compared with placebo (**Table 5**). There are no ongoing clinical trials in breast cancer or any other solid tumours. The benefit of targeting activin receptor signalling in solid tumours with bone metastasis clearly warrants further investigation.

Future agents targeting the osteoclast

Standard antiosteolytic treatments inhibit bone resorption by inducing osteoclast loss, with the adverse effect of hindering also bone formation. Novel agents with promising antiresorptive activity in animal models of myeloma and breast cancer are under investigation. Interestingly, some of these novel agents inhibit bone resorption while preserving bone formation. For example, the formation of the osteoclast sealing zone requires Dock5, a guanine nucleotide exchange factor for the small GTPase Rac, and C21, a chemical inhibitor of Dock5, reducing osteoclast-mediated bone resorption *in vitro*.[32] *In vivo*, C21 treatment of ovariectomised animals inhibits bone resorption and preserves bone formation. Under these experimental conditions, the BP alendronate severly impairs bone formation in ovariectomised animals, while inhibiting bone resorption.[32] Importantly, the pharmacological inhibition of Dock5 by C21 administration also protects mice against bone degradation in a model of bone metastasis caused by B16BL6 melanoma cells.[32]

The bromodomain and extraterminal (BET) protein inhibitors also hold a therapeutic promise in pre-clinical models of malignant osteolytic lesions.[33,34] The BET protein family (BRD2, BRD3, BRD4 and BRDT) is an important class of chromatin readers, regulating chromatin accessibility to transcription factors and RNA polymerase. For example, the treatment of animals with JQ1, a thienotriazolo-1,4-diazapine that binds selectively to BET bromodomain proteins, inhibits osteoclast differentiation by interfering with BRD4-dependent RANKL activation of NFATC1 transcription.[33] Moreover, JQ1 inhibits bone tumour outgrowth.[31] I-BET762 is another selective small molecule BET inhibitor that reduces myeloma cell proliferation, resulting in survival advantage in a myeloma xenograft model.[34]

TGF-β is a major bone-derived growth factor responsible for driving skeletal outgrowth of several types of solid tumours.[1] Several strategies designed to inhibit TGF-β signalling with receptor kinase inhibitors or neutralising TGF-β antibodies have been used to block experimental bone metastases.[1,26] However, to date, there are no clinical trials that study the effects of a TGF-β-related therapy for advanced cancer with bone metastases.

MicroRNAs have important roles in physiology and diseases and, more specifically, in bone metastasis.[35] This includes miR-34a, which was shown to inhibit osteoclastogenesis and bone resorption in animal models of osteoporosis and bone metastasis.[36] For example, the pharmacological administration of a miR-34a mimic delivered in nanoparticles can attenuate bone metastases in animals bearing breast or skin tumours.[36] In addition, miR-34a also enhances bone formation.[36] Hence, microRNA-based therapeutics may be a promising strategy to combat bone metastasis of cancers.

Conclusion

Bone-targeted treatments with BPs and denosumab are the standard of care for patients with skeletal metastases. In the early disease setting, for large subgroups of patients including men with hormone refractory prostate cancer and post-menopausal women or those receiving ovarian suppression therapy, there is evidence that BPs prevent the development of bone metastasis and prolong overall survival of patients with breast cancer. Treatment benefits of BPs do not, however, currently have regulatory approval for their adjuvant use in the early disease setting. On the same note, there is a survival benefit with zoledronate in patients with newly diagnosed multiple myeloma, supporting the early use of zoledronate, irrespective of the presence of bone disease. A better understanding of the molecular mechanisms behind improved survival of breast cancer patients who received BP therapy in a low oestrogen environment or those with multiple myeloma who received zoledronate clearly merits further investigation. Regarding denosumab, given that RANK and/or RANKL are expressed by tumour cells (breast, prostate, lung), there is a strong rationale for using this agent in an early setting. Indeed, the adjuvant treatment of nonmetastatic castration-resistant prostate cancer patients with denosumab delays the time to first bone metastasis and the time to first SREs. In the same vein, denosumab significantly delays the time to first clinical fracture in postmenopausal women with early breast cancer receiving adjuvant aromatase inhibitor therapy. Ongoing adjuvant trial DCARE in early breast cancer will provide further information on the clinical efficacy of denosumab on disease recurrence and survival benefit. Both BPs and denosumab have been associated with adverse effects, such as osteonecrosis of the jaw.[37] The incidence of osteonecrosis of the jaw in the oncology patient population is estimated between 1% and 15% and is not different between BPs and denosumab.[37] A better understanding of the mechanisms associated with osteonecrosis of the jaw will be necessary, especially if BPs and denosumab are given in a preventive setting.

Overall, BPs and denosumab are proven to provide a real clinical benefit to patients with metastatic bone disease. The use of these agents in a nonmetastatic setting warrants further pre-clinical and clinical investigation. Finally, the intense research in this area of oncology will lead to additional therapeutic options for the treatment of metastatic bone disease over the coming decade that exert both antiresorptive and anabolic effects.

Conflict of Interest

The authors declare no conflict of interest.

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