

Review

The Key Role of *Bisphosphonates* in the Supportive Care of Cancer Patients

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Abstract. *The present review aims at providing an assessment of the clinical significance of Bisphosphonates (BPs) in the treatment of patients with cancer. Materials and Methods: A systematic literature review was performed based on database search in PubMed/Medline and included articles up to August 2013. Results: BPs can reduce, delay, and prevent complications related to bone metastases. They improve mobility, functionality, pain, and quality of life. They limit survival of any inactive cancer cells in the micro-environment of the bone marrow, contributing to their death from anti-neoplastic treatments. Moreover, they limit and delay bone morbidity due to osteoporosis related to hormonotherapy in breast and prostate cancer. Finally, benefits can be derived from the combination of BPs with radiotherapy in bone density, recalcification, opioid use, and patient's quality of life and performance status. Conclusion:*

The contribution of BPs in the course of certain neoplasms is preventive and synergistic to other treatments.

It is well-known that the skeletal system functions as a calcium reservoir, offering support and protection of tissues and organs, contributing to numerous metabolic processes. Furthermore, the bone marrow in the skeletal system produces blood cells. Bone metabolism is a continuous chain of breakdown by osteoclasts and new synthesis by osteoblasts. The latter cells produce a matrix that becomes mineralized, a process induced by alkaline phosphatase generated by osteoblasts. During this process, some of the osteoblasts are trapped, forming bone cells. The main structural bone protein is type I collagen, which offers durability, and the mineral salt is hydroxyapatite, a form of calcium apatite with the formula $\text{Ca}_5(\text{PO}_4)_3$. The type and the degree of the crossing connections of the collagen fibres affect bone functions. In the case of a small number of connections, the helices can be divided and in the case of a large number of connections, the degree of energy absorption is reduced. The skeleton is a site of metastasis of numerous types of solid neoplasms. The most common are: breast and prostate (65%-75%), thyroid gland (60%), lungs (40%), urinary bladder (30%-40%), and kidney neoplasms (1, 2). Bone metastases appear in the last stage of neoplastic disease (3) and leads to multiple types of symptoms

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and complications (skeletal-related events, SREs), such as pain, pathological fractures requiring from conservative, minimally invasive techniques such as vertebroplasty (*e.g.* polymethyl methacrylate) (4) to classic surgical management or radiotherapy, spinal cord pressure, or hypercalcemia of malignancy (5-7). The bone lesions can be classified according to their radiologic appearance as osteoblastic, osteolytic, or mixed. Osteoclastic activity is increased in most metastases (including the characteristic osteoblastic metastases of prostatic cancer) (8). Since the pathological activation of osteoclasts plays a central role in the metastatic process, the action mechanism of bisphosphonic compounds primarily targets osteoclasts and secondarily the bone cells (9).

The Bisphosphonates (BP; also called diphosphonates) are derivatives of bisphosphonic acid, which is an analog of inorganic pyrophosphoric acid. They are strongly associated with phosphoric calcium and limit bone absorption (10, 11). This group of substances includes the following compounds: etidronate (ETI), tiludronate (TIL), clodronate (CLO), and the newer BPs which contain nitrogen such as pamidronate (PAM), alendronate (ALE), ibandronate (IBA), risedronate (RIS), and zoledronic acid (ZA). The strongest BPs (nitrogen-containing) act to inhibit the enzymes of the mevalonate/cholesterol biosynthesis pathway. The most important target-enzyme of BPs is farnesyl pyrophosphate synthase (FPPS). FPPS inhibition limits the synthesis of the isoprenoid compounds (farnesol and geranylgeraniol) necessary for the translation of the GTP-binding enzymes, such as RAB, RHO, and RAC, which participate in the osteoclasts' intracellular signaling. The concentration of the metabolite isopentenyl pyrophosphate (IPP), as a result of FPPS inhibition, may be responsible for the immuno-controlling effect on $\gamma\delta$ T-lymphocytes and may also lead to the production of another ATP metabolite with intracellular action (12).

The non-nitrogen-containing BPs are incorporated in the ATP of various compounds, limiting cellular functions (13). For example, ETI and CLO are incorporated in non-water-soluble ATP analogs, affecting ATP-dependent intracellular pathways. They induce the production of an ATP analog which facilitates cellular apoptosis (14). The nitrogen BPs affect and arrest the transmission of the cellular signal at the level of the small signaling proteins (*e.g.* RAS, RHO), which are essential for cellular function and survival (15, 16).

In the present review, we investigate the contribution of BPs in the overall treatment of oncologic patients. To our knowledge, this is the first study to investigate the effects of BPs in such a wide range of cancer settings.

Materials and Methods

A systematic literature review was performed based on database search in PubMed/MEDLINE and included articles up to September 2013. The terms used for the search were 'Biphosphonates', 'bone

metastasis' and synonyms combined with one or more of the following: 'osteopenia', 'osteoporosis', 'chemotherapy', 'radiotherapy', 'hormonotherapy', 'anti-tumoral effect' and synonyms. Furthermore, these terms were combined with the respective key words for each paragraph. Publications mentioned in the reference list found in the database search and considered suitable were manually searched for. Pre-clinical, clinical phase I, II, randomized phase III and IV studies, reviews, meta-analyses and abstracts of important meetings were analyzed. Articles published in English were mainly included.

Results

Bone metastases. The BPs can reduce, delay, and obviate complications associated with bone metastases, maintain mobility and functionality, and reduce pain (17-21).

Glucocorticoids combined with BPs and opioid therapy are indicated in cases of multifocal bone pain (22, 23). As anti-resorptive therapy, BPs and denosumab showed reduction and delay of bone events (3, 24-43). In addition, control of bone pain was achieved (17, 33, 44-45) with quality of life (QoL) preservation (45-49). Overall, it is a cost-effective treatment, taking into account the patient's QoL, the cost of the drugs, and the management of bone complications (50-53). Recently a combined analysis of three pivotal, randomised, phase III trials suggested that denosumab was superior to ZA in preventing SRE in patients with advanced cancer with bone metastases (54).

Breast cancer. Breast cancer metastatic cells mimic some features of normal osseous cells (osteomimetism), express osteoblastic or osteoclastic genes (55-57) and cause multiple types of complications (SREs) (27, 29, 58, 59). Metastases located in the spinal cord and the thoracic bones are associated with the highest rate of complications. On the contrary, those located in the skull bones are associated with the lowest rate of complications (60). The first studies that used BPs (PAM) assessed women with breast cancer and bone metastases (the Aredia Breast Cancer Study Group Protocols 18 and 19, in 1999) (61). There were fewer events in the group of women who had taken PAM in comparison to the placebo group (475 *versus* 648) and the time elapsed until radiotherapy was necessary to control pain was longer (62). Following these studies, three BPs (CLO, PAM, and ZA) gained approval for treatment of breast cancer bone metastases (30, 43). The prolonged (>24 months) administration of BPs reduced the incidence rate of SREs (p -value=0.020) in a retrospective study of 181 patients with breast cancer and bone metastasis. The occurrence of SREs was similar among the PAM (p =0.497), IBA (p =0.439), and ZA (p =0.552) (63). However recent data from an international randomized, double-blind study suggested that denosumab is more effective when compared to ZA for patients with breast cancer and bone metastases regarding time-to-skeletal events. It reduced the risk of multiple SREs

($p=0.001$) and the mean skeletal morbidity rate by 22% ($p=0.0004$) (64, 65).

Prostate cancer. ZA compared with placebo, when administered to patients with metastatic hormone-resistant prostate cancer, reduced by 36%; hazard ratio (HR) = 0.640; $p=0.002$ the incidence of bone events, and delayed the appearance of the first bone complication by more than five months ($p=0.009$) (59). In addition, it contributed to less pain in comparison to placebo (66). Benefit in pain relief for painful bone metastases was also shown by CLO (67-69) as well as substantial extension of the progression-free survival (PFS) ($p=0.066$) (68). Finally, IBA was also found to be effective in pain reduction in a small non-randomized study (70). According to a study presented at the Annual European Urology Congress in Paris in 2006 (71) and then published in two journals in 2007 (72) and 2010 (73), ZA administration is the treatment of choice in metastatic hormone-resistant prostate cancer. The appearance of bone events (SRE) is substantially reduced in pain-free patients administered BRs, suggesting the timely administration of the drug before pain manifestation because bone intactness is disturbed long before the appearance of pain. In a randomized trial of 311 men with metastatic prostate cancer, CLO improved OS *versus* placebo ($p=0.032$) (74). ZA (32) and denosumab are the two agents (FDA-approved) agents to prevent SREs in metastatic prostate cancer (75).

Lung cancer. In a double-blind placebo controlled randomized trial, ZA reduced the development of bone events by 31% (HR=0.693, $p=0.003$) in 773 patients with solid tumors [including 224 patients with non-small cell lung cancer (NSCLC) and 36 with small cell lung cancer (SCLC)] (61, 76). A total of 144 patients with NSCLC and symptomatic bone metastases were treated with ZA and were compared with 57 patients with asymptomatic bone metastases. The first arm had an improvement in median OS ($p<0.001$) and time-to-disease progression ($p<0.001$) (77). Preventive treatment with BPs for disease that likes to spread to the bones, such as lung cancer (78), can maintain QoL, reducing bone events and probably reducing the cost to health services (76). During the metastatic process of NSCLC to bone, the blood levels of type I collagen N-telopeptide was found to be increased in several patients. The administration of ZA caused a decrease of these levels, with simultaneous decrease of bone complications (79, 80).

Kidney cancer and other solid tumor types. Kidney cancer with lymph node disease is often accompanied by bone metastases (81). When ZA was administered to 46 patients suffering from renal cancer with bone metastases, it reduced the risk of bone complications by 58% (HR=0.418, $p=0.010$) and their incidence by 41% (HR=0.590; $p=0.011$). The

development of the first incident was delayed by one year in comparison to the placebo group (424 days *versus* 72, $p=0.007$) (27, 39). ZA in 74 patients with bone metastases secondary to renal cell carcinoma, reduced the skeletal morbidity rate ($p=0.014$), the risk of developing an SRE ($p=0.008$) and prolonged the time-to-first event ($p=0.006$) (82). ZA also led to a decrease in the complication rate in other types of cancer, such as thyroid cancer and urinary bladder cancer (27, 39). In solid tumours with bone metastases, the first bone incident (33% in the treatment group *versus* 43% in the placebo group) occurred within 314 days in the treatment group *versus* 168 days in the placebo group (27). Forty patients with bone metastatic bladder cancer received ZA and had an increased one-year survival rate *versus* the placebo group ($p=0.004$) (83). In 40 patients with recurrent solid tumors that did not present with bone metastases at baseline ZA increased bone metastasis-free survival at 12 and 18 months *versus* the placebo group ($p<0.0005$ and $p=0.0002$, respectively) (84). In 2008, Mystakidou *et al.* studied and compared the clinical responsiveness and safety of oral *versus* intravenous administration of IBA (85). Patients over 18 years of age suffering from solid tumours with bone metastases were studied. Clinical responsiveness was assessed by scintigram, radiology, and the concentration of C-terminal telopeptide of type-I collagen (S-CTX). The outcomes were comparable with regard to responsiveness, concentration decrease of S-CTX, pain assessment scales, functionality, and analgesic administration. IBA also led to satisfactory outcomes in colorectal metastatic disease (86).

Multiple myeloma. Patients in advanced stage of multiple myeloma may develop increased osteolytic activity by the osteoclasts and reduced osteogenesis by the osteoblasts. BPs such as CLO, PAM, and ZA, inhibit osteolysis, reduce the risk of bone events, improve pain (87) and potentially increase survival in patients with multiple myeloma (88). In patients undergoing initial chemotherapy for multiple myeloma ($n=94$), ZA improved 5-year OS *versus* chemotherapy alone ($p<0.01$) (89). In a published randomized trial (the MRC Myeloma IX trial, 2010) of patients aged over 18 years old in 120 UK centres, CLO was compared to ZA in patients with newly-diagnosed multiple myeloma who were or were not administered intensive induction chemotherapy. ZA substantially reduced bone morbidity increased the disease-free interval and the overall survival (progression-free and overall survival) in comparison to CLO. The survival benefit was significant and was associated with the reduction of bone complications and the clinical activity of BPs against the myeloma (41, 90). BPs as ZA are the pharmacological standard-of-care for patients with multiple myeloma (91, 92). BPs or denosumab are generally well-tolerated (93).

Potential anti-Tumor Effect

The time elapsed between the initial spread (dissemination or dispersion) of cancer cells and the appearance of metastases may exceed many years. Throughout this time period, the bone marrow may act as a shield for cancer cells which have spread from the primary cancer location (disseminated tumour cells, DTCs). In other words, the bone marrow may help DTCs to resist treatments. In this way, DTCs may re-appear after the end of treatment and cause recurrence of the disease (94). Because BPs are strong inhibitors of osteolysis, they can limit bone marrow invasion and the survival of any inactive cancer cells in the microenvironment of the bone marrow (95, 96). Paget supposed that modifying the microenvironment that supports cancer cell growth (the soil) may be equally important to treatment against the cancer cell itself (the seed) (57, 97). When BPs were used in pre-clinical trials, they had effects on cancer cells (seed) (98) that were: synergism with chemotherapy (99-112) inhibition of proliferation (95, 98, 101, 108, 113-117), invasion (114, 118, 119), adhesion (120, 121) and of migration (114, 118), and reduction of viability/induction of apoptosis (108, 122, 123). BPs had also pre-clinical effects on the microenvironment (soil) as inhibition of angiogenesis (14, 103, 108, 114, 117, 124-126) and immunomodulation (114, 127-132). It has also been proven in studies *in vitro*, as well as in animal model systems, that ZA inhibits, directly and indirectly, the development of cancer cells and the formation of solid tumours (103, 133, 134). These mechanisms of action can explain the improved outcomes in neoplasms, such as breast cancer and multiple myeloma when ZA was administered (94).

In clinical trials an increase in cellular apoptosis was observed when BPs were combined with anti-neoplastic treatments such as chemotherapy, hormonotherapy, radiotherapy and immunotherapy (monoclonal antibodies) (77, 83, 84, 89, 102, 105, 133-148).

Nitrogen-containing BPs render the bone marrow microenvironment less suitable for the growth of tumor cells (149). In the neoadjuvant setting ZA + chemotherapy *versus* chemotherapy-alone (n=205) reduced the size of the residual invasive neoplasm (p=0.006) and mastectomy rates (110). In the adjuvant setting in four phase I/II trials with 435 breast cancer patients, ZA reduced osseous microenvironment DTCs (57, 137, 139, 142, 143, 150). Data from three trials (ABCSG-12, ZO-FAST and AZURE) showed that bone marrow neoplastic cells may respond to ZA (57). In ABCSG-12, 1,803 pre-menopausal breast cancer cases were randomized to adjuvant tamoxifen or anastrozole with/without ZA (140). ZA prolonged (DFS) (p=0.01 at 48 months; p=0.009 at 62 months; p=0.021 at 76 months) and OS at 76 months (p=0.042) (140, 145, 151). The Zometa-Femara Adjuvant Synergy Trials (Z-FAST, ZO-FAST)

observed a ZA anticancer effect. In ZO-FAST, early ZA improved DFS *versus* delayed ZA (p=0.0314) in 1,065 patients during 36 months (144). In Z-FAST, early adjuvant ZA and letrozole reduced disease recurrence at 61 months in 600 post-menopausal women with early breast cancer (105). In the AZURE trial on 3360 premenopausal and post-menopausal patients with breast cancer (staged II/III), ZA improved DFS (p<0.05) and OS (p=0.017) in post-menopausal cases more than five years (110).

A meta-analysis (152) of 13 trials (136, 138, 140, 153-162) involved 6,886 patients with early breast cancer who were randomized to undergo adjuvant treatment with any BP (n=3,414) *versus* non-use (n=3,472). This meta-analysis showed no significant differences in terms of the overall number of deaths (p=0.079), bone metastases (p=0.413), overall disease recurrence (p=0.321), distant relapse (p=0.453), visceral recurrences (p=0.820), or local relapse (p=0.756) for the use or non-use of BPs.

There is not enough clinical evidence for the potential anti-tumor effect of ZA and further clinical trials are needed to prove its effect (152-164).

Preventive Use of BPs

BP limit and delay bone morbidity not only from complications of metastatic bone disease, but also in osteoporosis related to anti-neoplastic treatment (165, 166). ZA prevents bone density loss caused by hormonotherapy in patients with breast (166-170) and prostate cancer (175-181). Besides the bone damage that cancer may cause, there are significant consequences of anti-neoplastic treatments on bone health. This may very well be attributed to the endocrine disorders caused by these treatments, including ovarian suppression, androgen deprivation, and to aromatase inhibitors, which inhibit estrogen synthesis in post-menopausal women. With the increase in survival rates, achieved in recent years, the long-term adverse events of anti-neoplastic drugs on the skeleton constitute a significant problem (169). With the combination of cytostatic factors with BPs, the development and progress of bone participation in breast cancer can be substantially reduced. In addition, recent evidence suggests that there is an increase in patients' survival rate when BPs are administered in hormonotherapy (136, 171, 172).

Breast cancer. Menopausal women with early-stage breast cancer who receive anastrozole as hormonotherapy present an increased risk for osteoporosis and pathological fractures. The addition of RIS at a dosage for prevention and treatment of osteoporosis contributed to an increase in bone density in a time interval of 24 months (173). In invasive breast cancer with positive estrogen receptors, BPs administration reduced the risk of second primary cancer in the contralateral breast.

Table I. *Trials of combined treatment of bisphosphonates and RT.*

Reference	Patients (n)	Total/Dose, (Gy)	Bisphosphonate	Endpoint
Kouloulis <i>et al.</i> (183)	18	30 Gy × 10 fr	PAM	Radiologic response, increased bone density
Kouloulis <i>et al.</i> (184)	33	30 Gy × 10 fr	PAM	Radiologic response, improvement PS, QoL, biochemical markers
Kouloulis <i>et al.</i> (185)	42	30 Gy × 10 fr	PAM+RT vs. RT alone	Radiologic response
Micke <i>et al.</i> (186)	52	-	IBA	Increase bone density
Kaasa <i>et al.</i> (187)	376	8 Gy × 1 fr vs. 3 Gy × 10 fr	PAM	Control of bone pain, radiologic response
Vassiliou <i>et al.</i> (188)	45	30-40 Gy	IBA	Control of bone pain, increase bone density
Vassiliou <i>et al.</i> (189)	52	30-40 Gy	IBA	Radiologic response, increased bone density
Kijima <i>et al.</i> (192)	23	-	ZA+RT vs. RT alone	Increased bone density and SRE-free survival
Vassiliou V <i>et al.</i> (193)	18	-	ZA+RT	Control of bone pain, radiologic response, increased bone density
Ren <i>et al.</i> (194)	1585	-	-	Control bone pain
Vassiliou <i>et al.</i> (195)	32	30-40 Gy	IBA	Improvement bone density, recalcification QoL, PS Reduction of opioid use, pain scale
Atahan <i>et al.</i> (197)	100	30 Gy × 10 fr or 15 Gy × 5 fr	ZA	Efficacy - safety of RT combined with ZA

PAM: Pamidronate, CLO: clodronate, ZA: zoledronic acid, IBA: ibandronate, RIS: risedronate, PTH: parathyroid hormone, PS: performance status, QoL: quality of life, SRE: skeletal-related event, fr: dose fraction.

The specific outcome was directly related to the long-term administration of nitrogen-BP and ALE. There was a statistically significant risk reduction in comparison to patients who had not taken any related drug (174).

Prostate cancer. Randomized, controlled trials have demonstrated that ALE (175, 176), PAM (177) and ZA (178, 179) reduced ADT-related bone loss in patients with prostate cancer and severe osteopenia or osteoporosis (Z-score 2.7) under complete androgen deprivation (180). In a prospective sequential open-label study, it was found that the addition of trimestral *i.v.* CLO for preventing bone de-mineralization delayed the time-to-first bone metastasis ($p < 0.001$) compared to that of the patients who did not receive it. This was evaluated in 140 high-risk patients with prostate cancer and clinically organ-confined disease who had an increase in the prostate-specific antigen level after definitive treatment (181).

BPs and Radiotherapy

There are several indications that BPs may have additive or synergistic action with radiotherapy (105). The clinical effect of local radiotherapy in conjunction with BPs (Table I) was radiographically-confirmed in a series of trials (182-186). In women with painful bone metastases from breast cancer, a radiological response was also shown (187) in 88% of the patients when PAM was used in combination with 30 Gy external-beam radiation. In a randomized study (188), the use of IBA for painful bone metastases from solid tumors in combination with radiotherapy increased the control of bone pain, accelerating bone healing. There was a reduction in the pain scale from 6.3 to 0.8 and in the use of opioids from

84% to 24%. Statistically significant improvements were also noted in another study of patients suffering from different types of bone metastases (189). The average pain score for the lytic group was reduced from 8.1 to 1.5 points in three months. The corresponding reductions for the mixed and sclerotic groups were from 6.2 to 0.5 and from 4.4 to 0.3 points respectively. Complete pain responses were greater than 76.4% at all time points for all groups. Opioid consumption was also markedly reduced. Overall, the highest clinical response was noted for the lytic group, even though the mean values of pain, QoL and, KPS were worse than those of the other two groups at all time points (apart from pain score at 10 months). The percentage of patients of the lytic group experiencing a complete pain response was the least of the three groups during follow-up. At 10 months, bone density almost tripled for the lytic and almost doubled for the mixed group. In osteolytic lesions from breast cancer (in experimental animals), ZA in combination with radiotherapy increased the density, the micro-architecture, and the mechanical function in the areas of bone lesions (190). When a supplement of parathormone (as anabolic agent) was added (as a continuation of the same study), a significant increase in bone density and mass of the radiated bone was recorded (191). Kijima *et al.* investigated the rate of objective response and the SRE-free survival after combined therapy with radiotherapy and ZA for bone metastases from renal cell carcinoma (192). Combined therapy achieved a higher objective response rate and evidence of calcification ($p = 0.019$) and prolonged SRE-free survival than did radiotherapy alone ($p = 0.003$). In 2009, Vassiliou *et al.* also used this combined treatment (ZA and radiotherapy) for metastatic bone disease from renal cancer

(193). There was a considerable pain response at three months, with the mean pain score decreasing from 9.1 to 1.1 points ($p<0.001$). Notably, eight out of 18 patients (44%) had a complete and the remainder a partial pain response. At 10 months of follow-up, the mean pain score was further reduced to 0.6 points, with 13 out of 18 (72%) patients having a complete, and two (11%) a partial pain response. The pain response was accompanied by a marked reduction in the opioid analgesic consumption, with the mean decreasing from 129.1 mg at baseline to 30 mg at study end ($p<0.001$). There was also a significant improvement in patients' KPS and QoL, with the mean scores increasing from 62.8 and 43.2 at baseline to 87.1 and 90.4 at 10 months respectively ($p<0.001$). The radiological assessment showed a marked increase in the average bone density of irradiated lytic bone lesions, increasing from 86.5 HU at baseline, to 132.3 HU at three months (52.9% increase), and to 262.3 HU (203.2% increase) at the evaluation at ten months.

In a review of the current literature (22 studies with 1585 patients), the efficacy and safety of the combination of *i.v.* BP with radiotherapy was compared to radiotherapy-alone and was found to be superior in pain relief with acceptable toxicity (194). In a prospective phase II study (195), the efficacy of combined radiotherapy and IBA in patients with breast cancer and metastatic bone disease was investigated. It was shown that the main advantages of the combined administration of BP with radiotherapy were the following: mean bone density improvement (increased by 42.9% at three months and by 83.1% at 10 months, $p<0.001$); reduction of opioid need, since at baseline 62.5% of patients were on opioid analgesics, with this percentage being 12.5% three months thereafter; at the time points of six and ten months, no patient required opioid analgesics for pain alleviation (at all time points $p<0.001$); reduction in the pain scale from 5.1 at baseline to 0.8 points at three months, with further reductions at later time points (all $p<0.001$ compared to baseline); improvement in the patient's QoL and KPS in the corresponding mean scores EORTC-QOL-physical functioning scale and KPS index by 35.2 and 17.4, respectively. There is a synergistic activity that results in improved bone stability, micro-architecture, and increased mechanical strength (196). In a phase IV prospective randomized clinical study, it was found that a reduced-dose radiotherapy course (15 Gy in five fractions) when used concomitantly with ZA produces similar response rates and response durations to a high-dose radiotherapy regimen (30 Gy in 10 fractions) in patients with painful breast cancer bone metastases (197). No statistically significant differences were observed in time-to-first SRE ($p=0.41$), time-to-response (either partial or complete) time-to-treatment ($p=0.27$), time-to-complete response ($p=0.20$) and duration of response ($p=0.15$). Twenty seven patients with bone metastases secondary to renal cell carcinoma underwent

radiotherapy with or without ZA. Radiotherapy with ZA prolonged SRE-free survival ($p=0.047$) and duration of pain response ($p=0.047$) compared with radiotherapy alone (198).

Discussion

BP can reduce, maintain mobility and functionality, and prevent complications related to bone metastases in the following types of cancer: Breast (PAM, ZA, IBA), prostate (CLO, ZA), lung (ZA), renal (ZA), thyroid-bladder (ZA), colo rectal (IBA), multiple myeloma (CLO, ZA) (In detail see also Table II). In addition, control of bone pain was achieved along with QoL preservation.

Because BPs are strong inhibitors of osteolysis, they can limit bone marrow invasion and the survival of any inactive cancer cells in the micro-environment of the bone marrow. They show synergism with anti-neoplastic treatments (chemotherapy: CLO, ZA, IBA; hormonotherapy: CLO, ZA; radionuclide therapy: ZA; radiotherapy: PAM, ZA, IBA) contributing to malignant cell apoptosis. From the combination of BP with radiotherapy, clinical benefits such as bone density improvement, increase of re-calcification at the involved area, reduction of opioid use, reduction in pain scale and improvement in the patient's QoL and KPS, can be derived.

BPs limit and delay bone morbidity of osteopenia related to anti-neoplastic treatments, such as hormonotherapy (complete androgen deprivation, anastrozole) in patients suffering from breast cancer and prostate cancer (PAM, CLO, ZA, RIS, ALE).

An increase in overall survival rates was demonstrated in cancer with bone metastasis such as prostate (CLO), lung (ZA), and multiple myeloma (PAM, CLO, ZA), and in progression-free survival in metastatic prostate cancer (CLO).

The indication for BPs use should always be evaluated even if the patient is 'pain free' or at an early stage of the disease (199) because they could maintain bone health in patients with cancer and represent a supplemental treatment for those at advanced stages (149). Overall, it is a cost-effective treatment, taking into account the patient's QoL, the drug costs and the management of the bone complications.

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Table II. Clinical benefits for individual Bisphosphonates.

Bisphosphonate	Clinical benefit (ref)
PAM	↓SREs in breast Ca-bone M (61, 62, 63), MM (87), ↑OS in MM (87, 88) ↑Cellular apoptosis - synergism with anti-neoplastic treatments: RT (183-185,187). ↓Anticancer treatment induced osteopenia in breast cancer (177)
CLO	↓SREs in prostate Ca-bone M (67-69), multiple myeloma (87) ↑PFS in prostate Ca-bone M (68) ↑OS in prostate Ca-bone M vs. placebo (74),MM (87, 88) ↑Cellular apoptosis- synergism with antineoplastic treatments: Chemotherapy (136, 138, 146), hormonotherapy (136, 138, 146). ↓Anticancer treatment-induced osteopenia in breast (136), prostate cancer (181)
ZA	↓SREs in metastatic breast Ca (63), prostate Ca (32, 59, 66, 71, 73), lung Ca (61, 76, 78, 80), renal Ca (27, 39, 82), thyroid, bladder Ca (27, 39), MM (87, 41, 90) ↑OS, TTP in lung Ca-bone M, MM (87, 88), ↑1 year survival rate in bladder Ca-bone M vs. placebo (74) ↑Cellular apoptosis - synergism with antineoplastic treatments: chemotherapy (57, 77, 84, 89, 102, 110, 139, 141, 144, 145, 148, 152), radionuclide therapy (135), hormonotherapy (105, 137, 141, 144, 145), RT (105, 190-193, 197, 198) ↓Anticancer treatment induced osteopenia in breast cancer (166-168, 178, 179) ZA, Denosumab: FDA approved to prevent SREs in metastatic prostate cancer (32, 75)
IBA	↓SREs in breast Ca-bone M (63), prostate Ca-bone M (70), various solid tumors-bone M (85), in colorectal bone M (86) ↑Cellular apoptosis - synergism with anti-neoplastic treatments: Chemotherapy (147), RT (188, 189, 195)
RIS	↓Anticancer treatment induced osteopenia in breast cancer (170, 173)
ALE	↓Anticancer treatment induced osteopenia in prostate (175, 176)

PAM: Pamidronate, CLO: clodronate, ZA: zoledronic acid, IBA: ibandronate, RIS: risedronate, ALE: aledronate, SREs: skeletal related events, Ca: cancer, M: metastasis, MM: multiple myeloma, OS: overall survival, TTP: time-to-progression, PFS: progression-free survival, RT: radiotherapy.

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