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Bisphosphonates for the treatment of patients with cancer

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ABSTRACT

Bisphosphonates inhibit osteoclasts activity and therefore reduce bone resorption. The main application of bisphosphonates in patients with cancer involves treatment of hypercalcemia, prevention of cancer treatment-induced bone loss, and decrease of the risk of skeletal-related events in patients with breast cancer or prostate cancer and bone metastases. For some time now there has been an increasing amount of data indicating that treatment with bisphosphonates improves survival of patients with early breast cancer. The activity is restricted to postmenopausal women or premenopausal patients whose treatment involves gonadotropin agonist.

Key words: bisphosphonates, breast cancer, prostate cancer

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Introduction

Bisphosphonates (BPs) are synthetic analogues of naturally existing pyrophosphate. The first bisphosphonate was developed in the 19th century [1]. It was primarily used in the chemical industry as an anticorrosive and anti-scaling agent. The ability of BPs to slow down a breakout of hydroxyapatite was discovered in the 1860s. In 1969 the first BP was used in medicine in a man with myositis ossificans.

BPs differ in chemical structure — they are divided into two classes: BPs of the first generation (or simple BPs), which do not contain nitrogen; and nitrogen-containing BPs of the second or third generation. This classification correlates with the ability of BPs to inhibit bone resorption and is related to different mechanisms of action (Tab. 1).

Basic mechanism by which BPs inhibit bone resorption results from their very high affinity to mineral components of bone and binding with hydroxyapatite crystals. BPs are captured by bones selectively and built in areas of the bone's active rebuilding. The remaining BPs are excreted by urine. The amount of BPs that bind to bones relates mainly to the intensity

of bone turnover, the route of administration, and the affinity of BPs to react with bone structure. Activated osteoclasts brake down the bone-matrix on the surface of bones, and therefore induce the release of bone-derived constituents, including BPs, which are absorbed by osteoclasts. The accumulation of end products of BP metabolism in osteoclasts induces its apoptosis and therefore inhibits bone resorption [2]. The newer BPs have also an ability (in vitro) to inhibit proliferation, invasion, and migration of cancer cells, to induce apoptosis of cancer cells, to inhibit neoangiogenesis, to activate of T $\gamma\delta$ lymphocytes, and to modulate macrophage and osteoblast activity [3].

The most important areas of BP usage in oncology are:

- treatment of hypercalcaemia (this article does not elaborate on that);
- inhibition of cancer treatment-induced bone loss (CTIBL);
- reduction of the risk of skeletal-related events (SRE) or delay of their occurrence in patients with bone metastases;
- reduction of the risk of cancer recurrence and mortality after definite treatment.

Table 1. Classification of bisphosphonates

Subclass	Generation	Drug	Force	Mechanism of action
Non-nitrogen containing or "simple"	First	Etidronate	1	ATP-dependent
		Clodronate	10	
		Tiludronate	10	
Nitrogen containing	Second	Alendronate	100	Inhibition of farnesyl pyrophosphate synthase
		Pamidronate	100–1000	
		Ibandronate	1000–10 000	
	Third	Risedronate	1000–10 000	
		Zoledronic acid	> 10 000	

BP in patients with breast cancer

A prevention of CTIBL

In premenopausal women diagnosed with breast cancer, systemic treatment can induce a secondary loss of ovarian function (e.g. after chemotherapy) or may directly suppress ovarian function by hormonal blockage with luteinising hormone releasing hormone analogue (aLHRH). Long-lasting oestrogen deficiency has a profound effect on bone health. In women in whose treatment induced premature menopause, both permanent (after chemotherapy) or temporary (during aLHRH treatment), the assessment of bone fracture risk by bone densitometry is recommended. Furthermore, a concentration of serum calcium, 25-OH-vitamin D, or parathyroid hormone as secondary causes of osteoporosis should be evaluated. It is recommended to advise a calcium-enriched diet (1000 mg every day), vitamin D (1000–2000 units every day), and to change lifestyle habits by taking more weight-bearing exercise, quitting smoking, and reducing alcohol consumption. In cases when bone-mineral density is reduced (e.g. T-score < -2) a therapy of BP should be considered [4]. Clodronate and risedronate are active in the prevention of bone resorption in premenopausal women; however, most data come from trials with zoledronic acid (4 mg intravenously every six months). Zoledronic acid is therefore recommended to prevent bone loss.

In postmenopausal women treated with aromatase inhibitor (IA) bone health should be monitored for risk of fracture by bone densitometry and other diagnostic tools, e.g. the FRAX (Fracture Risk Assessment Tool) algorithm designed by the WHO (World Health Organisation), which unfortunately does not include antineoplastic treatment as a specific risk factor of bone loss. General recommendations involve supplementation of calcium and vitamin D, as well as a change in lifestyle (as mentioned above). Anti-resorptives should be considered in patients with T-score < -2 or in those having at least two risk factors of bone fracture, e.g.

Table 2. Anti-resorptive drugs for the prevention of CTIBL in postmenopausal women with breast cancer

Bisphosphonates	Ibandronate 150 mg <i>p.o.</i> every month
	Clodronate 1600 mg <i>p.o.</i> every day
	Risedronate 35 mg <i>p.o.</i> every week
	Alendronate 70 mg <i>p.o.</i> every week
	Zoledronic acid 4 mg <i>i.v.</i> every 6 months
Anti-RANKL	Denosumab 60 mg <i>s.c.</i> every 6 months

age < 65, T-score < -1.5, active cigarette smoking, BMI (body mass index) < 24, long-term (> 6 months) glucocorticoid consumption, bone fractures in age > 50 years, or positive family history of osteoporosis [4]. In women with cancer treated with IA, some agents have demonstrated activity in reducing the risk of CTIBL (Tab. 2) [5–10]. The activity of denosumab is not the subject of this article.

Therapy with BP in patients with breast cancer and bone metastases

In 2012 a Cochrane database meta-analysis revealed that therapy with BPs compared with no BPs in women with breast cancer and bone metastases reduces the risk of SRE by 15% [RR (relative risk) 0.85; 95% CI 0.77–0.94; *p* = 0.001], increases the median time to occurrence of SRE, decreases bone pain, and improves quality of life [11]. Overall survival is not affected by the therapy. Either ibandronate (oral and intravenous), clodronate, pamidronate, or zoledronic acid were effective. Reduction of the risk of SRE varied from 14% for oral ibandronate, 23% for intravenous pamidronate, up to 41% for zoledronic acid; however, those differences should not influence clinical practice. It should be emphasised that pamidronate and zoledronate are the only intravenous BPs whose clinical effectiveness has been proven in many end-points.

In a phase III non-inferiority trial carried out on breast-cancer patients with bone metastases and on

patients with multiple myeloma, pamidronate had similar efficacy to zoledronic acid [12]. In another phase III non-inferiority ZICE trial, the effectiveness of oral ibandronate was inferior to zoledronic acid in reducing the risk of SRE [hazard ratio (HR) 1.15; 95% CI 0.967–1.362; $p = 0.017$]; however, the ability to delay the first SRE was similar [13].

The influence of BPs on a risk of SRE seems to be related to duration of BP therapy and becomes noticeable few months after the first administration [14]. Moreover, some retrospective data revealed that occurrence of the first SRE before the initiation of BP therapy increased the risk of subsequent SREs (HR 2.08) during BP treatment [15]. According to ASCO (American Society of Clinical Oncology) experts, it is recommended that BP is started in all patients with breast cancer as soon as bone metastases are diagnosed [16].

In the Cochrane meta-analysis, the influence of BPs on the efficacy of standard systemic treatment of disseminated breast cancer without clinically evident bone metastases was evaluated. The results suggest that the BPs neither reduced the incidence of bone lesions nor improved overall survival (OS) [11].

The role of BPs in the adjuvant setting

Pre-clinical data suggested that BPs may have an anti-tumour effect. This is what caused the launch of clinical trials with BPs in addition to standard adjuvant treatment in prevention of breast cancer recurrence. One of the first substances analysed was clodronate. Some trials revealed a positive [17, 18], and the other a negative [19] impact of clodronate on OS (HR, respectively: 0.38, 0.77, and 1.94). In the most recent trial, NSABP B34, which recruited larger numbers of patients, clodronate did not reduce the risk of cancer recurrence (HR 0.91; 95% CI 0.78–1.07; $p = 0.27$) or risk of death (HR 0.84; 95% CI 0.67–1.05; $p = 0.13$) [20]. In a subgroup analysis, women over 50 years old treated with BP had lower risk of cancer recurrence (HR 0.75; 95% CI 0.57–0.99; $p = 0.045$). Meta-analysis of the trials showed that therapy with clodronate did not improve OS (HR 0.84; 95% CI 0.56–1.26; $p = 0.4$), bone metastases-free survival (HR 0.77; 95% CI 0.58–1.02; $p = 0.07$), or extra-skeletal metastases (HR 0.89; 95% CI 0.61–1.3; $p = 0.55$) [21]. Possibly, the results of the meta-analysis were determined by a small ($n = 282$), negative trial carried out by Saarto et al. in the 1990s [19].

The effectiveness of some BPs of the second generation — ibandronate and pamidronate — in comparison to placebo in early breast cancer (node positive or node negative) was evaluated in two phase III trials. In the GAIN trial with ibandronate there were no differences with reference to disease-free survival (DFS) (HR 0.95; 95% CI 0.77–1.16; $p = 0.59$) or OS (HR 1.04; 95% CI

0.76–1.42; $p = 0.83$) [22]. Similarly, in the second trial with oral pamidronate, no positive impact on bone recurrence-free survival (HR 1.03; 95% CI 0.75–1.4; $p = 0.86$) or on OS (no numbers reported) was observed [23].

The AZURE trial recruited patients with stage II or III breast cancer (with or without ER expression). A combination of zoledronic acid with a standard adjuvant treatment did not influence DFS (HR 0.94; 95% CI 0.82–1.06; $p = 0.3$) or OS (HR 0.93; 95% CI 0.81–1.08; $p = 0.37$) [24]. However, zoledronic acid decreased the risk of metastatic bone lesions (HR 0.81; 95% CI 0.68–0.97; $p = 0.022$). An exploratory analysis suggested that the positive effect of BP was restricted to a cohort of women who passed through menopause at least five years before diagnosis (31% of the whole trial population). In this subgroup, an improvement in invasive disease recurrence-free survival was observed (HR 0.77; 95% CI 0.63–0.96; $p = 0.03$).

The ABCSG-12 trial was conducted in premenopausal women with early (stage I–II) breast cancer treated with ovarian suppression therapy and tamoxifen or anastrozole. Concomitant treatment with zoledronic acid every six months for three years improved DFS (HR 0.77; 95% CI 0.6–0.99; $p = 0.042$), while the impact on OS was non-significant (HR 0.66; 95% CI 0.43–1.02; $p = 0.062$) [25]. An important difference between the two above-mentioned trials is that in the ABCSG-12 trial patients had complete hormonal suppression, so the population resembled the postmenopausal subgroup form of AZURE. The reduction of disease recurrence was similar between the trials (HR 0.77).

The third trial, ZO-FAST, investigated the role of a combination of zoledronic acid and five-year adjuvant hormone therapy with letrozole in postmenopausal women with breast cancer stage I–III. A control arm consisted of hormone therapy, but BPs were introduced in cases of clinical indications (bone fracture, bone density loss) [9]. The trial reported a reduction of relative risk of disease recurrence by 34% (95% CI for HR: 0.44–0.97; $p = 0.037$), which did not translate into gain in OS (HR 0.69; 95% CI 0.42–1.14; $p = 0.15$). An explorative analysis suggested that women older than 60 years or those who passed menopause at least five years before diagnosis could benefit in OS (HR 0.5; $p = 0.022$).

To establish the role of adjuvant BPs, an individual-patient data meta-analysis of 19,000 women with early breast cancer involved in 26 clinical trials was conducted [26]. It suggests that administration of BPs decreased the relative risk of bone recurrence by 17% (95% CI for HR: 0.73–0.94; $p = 0.004$), and less clearly decreased the risk of death (RR 0.91; 95% CI 0.83–0.99; $p = 0.04$) or risk of distant recurrence (RR 0.92; 95% CI 0.85–0.99; $p = 0.03$). In a subgroup analysis, there were no differences in effect irrespective of steroid receptor

expression, regional lymph node involvement, or histological malignancy grade. The benefits of BPs therapy may be restricted mainly to women over 55 years or those with established menopause. Among postmenopausal women, adjuvant BP decreased the relative risk of recurrence by 28% (95% CI for HR: 0.6–0.86; $p = 0.0002$) and relative risk of breast cancer death by 18% (95% CI for HR: 0.73–0.93; $p = 0.0002$). It was transferred to 3% of absolute gain in the percentage of patients alive after 10 years of follow-up (18% vs. 14.7%).

In the SWOG S0307 trial clodronate, ibandronate, and zoledronic acid were investigated in an adjuvant setting. No differences between BPs were observed in DFS or OS outcomes [27]. There is insufficient evidence to recommend alendronate, risedronate, or etidronate in the management of early breast cancer.

According to ESMO (European Society of Medical Oncology) recommendations, BPs (clodronate or zoledronic acid) should be considered in adjuvant treatment of postmenopausal women or in premenopausal women with hormonal blockage (aLHRH) [28]. It should be mentioned that BPs have no regulatory approval in this indication. It is suggested that the therapy be initiated simultaneously with standard adjuvant treatment. The optimal duration of adjuvant BPs is still unknown, but it seems that it should last for 3–5 years, as it was administered in trials. In premenopausal women treated with aLHRH BPs should accompany only the ablation period, unless there are indications to continue BPs longer (e.g. low T-score).

BPs in prostate cancer

Prevention of CTIBL

Hormone therapy, both adjuvant and palliative, can change bone metabolism in men with prostate cancer. As a consequence, men with androgen deprivation therapy have higher risk of bone loss. The ESMO recommends an assessment of risk of bone-loss before initiation of hormone therapy by bone densitometry. Furthermore, it is suggested that secondary causes of bone loss be evaluated, e.g. serum calcium, parathyroid hormone, and 25-OH-vitamin D concentration. Furthermore, it is advised that supplementation of calcium (1000 mg/day) and vitamin D (1000–2000 IU/day) be initiated, as well as moderate exercises, constrained alcohol consumption, and smoking cessation [4]. Anti-resorptives should be considered in patients with T-score < -2 or when at least two risk factors of osteoporosis occur (e.g. age > 65 years, T-score < -1.5 , cigarette smoking, BMI < 24 , long-term steroid intake, bone fractures over 50 years old, positive family history for osteoporosis) [4]. The substances active in this situation are mentioned

Table 3. Anti-resorptive drugs for the prevention of CTIBL in patients with prostate cancer

Bisphosphonates	Pamidronate 60 mg <i>i.v.</i> every 12 weeks
	Risedronate 35 mg <i>p.o.</i> every week
	Alendronate 70 mg <i>p.o.</i> every week
	Zoledronic acid 4 mg <i>i.v.</i> every 6 months
Anti-RANKL	Denosumab 60 mg <i>s.c.</i> every 6 months

in Table 3. Denosumab is the only anti-resorptive that has regulatory approval in this indication. BPs can be prescribed only off-label [29–32].

Castration-sensitive prostate cancer with bone metastases

The effectiveness of first-generation BP in patients with hormone-sensitive prostate cancer with bone metastases was investigated in the MRC PR05 trial. The primary end-point of the trial was not met — HR for symptomatic bone progression-free survival was 0.79 ($p = 0.66$). In post-hoc analysis an improvement in OS was found — five-year survival rates were higher in hormonal therapy with BP group than in the group with hormonal therapy alone (30% vs. 21%; R 0.77; $p = 0.032$) [33, 34]. Although the result was statistically significant, it did not influence clinical practice, mainly due to the character of the mentioned analysis and primary positive results with more potent BP — zoledronic acid.

The CALGB 90202 study recruited men with prostate cancer with bone metastases, and early initiation of zoledronic acid did not reduce the risk of SRE (HR 0.77; $p = 0.39$) compared with such treatment delayed until the development of castration resistance [35]. Moreover, there was no positive impact of zoledronic acid on PFS (HR 0.89; $p = 0.22$) or OS outcome (HR 0.88; $p = 0.29$).

In the STAMPEDE trial, one of several arms of treatment evaluated the efficacy of zoledronic acid in men with hormone-sensitive prostate cancer undergoing standard hormonal treatment. There were no differences in OS (HR 0.94; $p = 0.45$), failure-free survival (HR 0.92; $p = 0.2$), or time to SRE (HR 0.89; $p = 0.22$) compared with hormonal therapy alone. The BP did not influence prognosis also in the metastatic subgroup [36]. In another arm of the trial a combination of hormonal therapy, docetaxel, and zoledronic acid was evaluated. The efficacy of the combination therapy did not differ from hormonal therapy plus docetaxel (HR for OS 1.06; $p = 0.59$).

A meta-analysis of trials with BPs in castration-sensitive prostate cancer was published in 2016. Its results suggested an improvement in OS (HR 0.88; 95% CI 0.79–0.98; $p = 0.025$) among men with metastatic dis-

ease with an increase in four-year survival rate by 5%. After excluding data from the MRC PR05 trial with clodronate, the effect became insignificant (HR 0.94; 95% CI 0.83–1.07; $p = 0.32$) [37]. In a subgroup of patients with locally advanced disease, meta-analysis did not show any difference in OS in patients treated with clodronate (HR 1.03; 95% CI 0.89–1.18; $p = 0.72$) or with zoledronic acid (HR 0.98; 95% CI 0.82–1.16; $p = 0.78$).

Castration-resistant prostate cancer (CRPC)

There are no data supporting the use of zoledronic acid in locally advanced CRPC — the ZOMETA 704 trial was terminated early because of low event rates (smaller than expected).

In phase III trials in bone-metastatic CRPC neither pamidronate nor clodronate proved to be more effective than placebo in cases of bone pain or SRE [38, 39].

Higher activity of zoledronic acid in patients with CRPC and bone metastases was demonstrated in the ZOMETA 039 trial and led to the registration of the only BP in this indication. Therapy with zoledronic acid (4 mg every three weeks) compared to placebo was more effective in reduction of SRE rate after 24 months of treatment. The proportion of patients with at least one SRE was 38% in the group of patients treated with zoledronic acid and 49% in the control group ($p = 0.028$). Median time to first SRE was increased (by approximately six months) in the BP arm (HR 0.68; $p = 0.009$), and the cumulative risk of SRE was reduced (HR 0.68; 95% CI 0.49–0.84; $p = 0.002$) [40]. The benefits of BP did not translate into risk of progression or quality of life. An analgesic effect was observed only in patients who had initiated the treatment with 8 mg of zoledronic acid ($p = 0.026$) [41].

BPs were evaluated also in an adjuvant setting after local treatment of prostate cancer. Neither clodronate (MRC PR 04 trial) nor zoledronic acid (ZEUS trial) decreased the risk of bone metastases [22–42].

In conclusion, there are several applications of BPs in prostate cancer:

- reduction of risk of SRE in men with CRPC and bone metastases (zoledronic acid);
- decrease of risk of CTIBL in men with risk factors of osteoporosis undergoing palliative or adjuvant hormonal therapy.

It should be emphasised that there are no data supporting the use of BPs in the prevention of SRE in men with prostate cancer and bone metastases before development of CRPC.

Dosage of BPs in cancer patients with bone metastases

The proper dosage of clodronate (1600 mg orally every day) and pamidronate (90 mg in a two-hour infu-

sion every 3–4 weeks) in women with metastatic breast cancer was established in clinical trials.

Zoledronic acid (4 mg in a 15-min. infusion) should be administered every 3–4 weeks in patients with bone-metastatic cancer. The results of two randomised clinical trials comparing standard dose of zoledronic acid with a regimen with longer intervals were published in 2017. Zoledronic acid (4 mg) every 12 weeks was as effective as the BP every four weeks with regard to reduction of the risk of SRE in patients with breast cancer, prostate cancer, and multiple myeloma [45, 46].

Summary

Bisphosphonates in the treatment of patients with cancer are used for three main reasons. The most intriguing one is their antineoplastic activity. However, the efficacy of BPs in this setting is limited to patients with early breast cancer after menopause or those receiving inhibition of ovary function — adjuvant BPs reduce the risk of recurrence and improve survival. The second and best-known reason is to decrease of symptoms or signs related to cancer, e.g. pain, hypercalcaemia, and SRE — the most significant data regarding SRE were collected in patients with breast, prostate cancer, and multiple myeloma. The third purpose of therapy is prevention or alleviation of cancer treatment-related adverse effects — it is documented in clinical trials that BPs administered in women with breast cancer, and also in men with prostate cancer, decrease the risk of CTIBL in the course of hormonal therapy.

BPs are generally well tolerated drugs, but some side effects are typical for the class. The most important adverse events are: reactions of acute phase (up to 25–30% in patients who receive intravenous infusions), exacerbation of bone pain, hypocalcaemia, kidney insufficiency (BPs should be administered with caution if creatinine clearance is < 30 ml/min), acute osteonecrosis of the jaw (up to 1.5% of patients who receive BPs intravenously), atypical femoral fractures, and gastrointestinal disorders (mostly after oral BPs).

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