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Bisophosphonates in the treatment of osteoporosis in women with breast cancer

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Abstract
Osteoporosis is the most common skeletal disorder. It is characterized by a decrease in bone density, which results in a greater likelihood of hip, vertebral and long bone fractures. Women who are undergoing hormonal treatment for hormone-related breast cancer are particularly at risk for osteoporosis. Among women diagnosed with premenopausal breast cancer, therapeutic activities may result in secondary loss of ovarian function or include complete hormonal blockade.
Long-term reduction of estrogen concentration adversely affects bone metabolism. It is recommended to assess the risk of bone fractures with densitometry in patients with hormone blockade effects. Calcium and vitamin D supplementation, moderate exercise is recommended. If bone mineral density is reduced, consideration should be given to initiating bisphosphonate therapy.
Bisphosphonates inhibit bone resorption mediated by osteoclasts. The most important is the division into two classes: compounds containing no nitrogen (called simple bisphosphonates) and containing nitrogen. This division carries a significant difference in the strength of bone resorption inhibition and a different mechanism of action.

Key words: breast cancer, osteoporosis, bisphosphonates

Admission

The skeleton is one of the largest organs of the human body. It performs functions such as movement, support, protection of internal organs. The skeleton also contributes to maintaining normal homeostasis of the whole body and the maintenance of many important organs / systems other than bone. It also has the functions of a reservoir of minerals such as calcium and phosphorus, which can be released when the body's demand increases. Bone tissue can produce various substances such as proteins, peptides, including growth factors, chemokines, cytokines. Osteoporosis is the most common skeletal disorder. It is characterized by a decrease in bone density, which results in a greater likelihood of hip, vertebral and long bone fractures. Women who are undergoing hormonal treatment for hormone-related breast cancer are particularly at risk for osteoporosis. Osteoporosis is treated with vitamin D3 and calcium supplementation, an appropriate dose of systematic movement as well as bisphosphonate drugs. [1]

Drugs used in women with hormone-dependent breast cancers have side effects, including osteoporosis. About two-thirds of all breast cancer patients are dependent on hormones, estrogen receptors or progesterone receptors that are expressed by cancer cells. Therefore, hormone therapy is an important option in adjuvant treatment using two mechanisms: To prevent the interaction of cancer cells with estrogen receptors by using selective estrogen receptor modulators (SERMs) and inhibiting the transformation of androgen tissues into estrogen with aromatase inhibitors. [2]

There are other potential treatments for or prevention of breast cancer in addition to cytotoxic therapy, in particular with hormone therapy. Most breast cancers express the estrogen receptor (ER) and are driven by the female estrogen hormone. These "ER-positive" cancers can be effectively treated by significantly reducing the natural level of estrogen, eg by removing a woman's ovaries or stopping them from producing estrogen with an aromatase inhibitor (AI) that blocks the pathway through which estrogen is produced, or blocking the estrogen receptor , e.g., selective estrogen receptor modulators such as tamoxifen. [2]

Tamoxifen, one of the selective estrogen receptor modulators, used as standard care in the adjuvant treatment of breast cancer. Adjuvant treatment of breast cancer had a better response due to aromatase inhibitors compared to tamoxifen. Aromatase inhibitors resulted in reduced estrogen production, resulting in a reduced risk of cancer recurrence in postmenopausal women diagnosed with breast cancer.

Third-generation aromatase inhibitors, anastrozole, letrozole and exemestane are recently used in first-line hormone therapy in these women. However, these aromatase inhibitors significantly increase bone turnover markers and are responsible for accelerated bone loss, resulting in increased fracture rates. As advances in the treatment of breast cancer in postmenopausal women have led to long-term survival improvement, increased bone loss and fracture risk should be particularly prevented in this patient group. [2]

Bisophonates inhibit bone resorption by osteoclasts by attaching to hydroxyapatite binding sites on the bone surface. Bisphosphonates have a high affinity for metallic surfaces such as iron oxide. The basic mechanism - inhibition of bone resorption - is due to their very high affinity for bone mineral components. This inhibits pyrophosphate-using enzymes. Bisphosphonates reduce osteoclast activity, reducing the development and recruitment of osteoclast progenitor cells and promoting osteoclast apoptosis. Due to the excellent binding properties of hydroxyapatite and metallic surfaces and their good safety profile, bisphosphonates have been evaluated as formulating agents, especially for steric stabilization of nanoparticles. From a chemical point of view, these drugs consist of two phosphonate groups connecting to a central carbon atom, the P - C - P backbone structure allows

bisphosphonate binding to divalent metal ions such as Ca 2+ 5, resulting in bisphosphonates binding to hydroxyapatite (HAP) in vivo 6 and inhibits the dissolution of hydroxyapatite crystals. Hydroxyapatite is the main mineral component of teeth and bones. Synthetic hydroxyapatite is widely used in many areas because of its much lower cytotoxicity and biocompatibility. Therefore, interaction studies between hydroxyapatite and a bisphosphonate are very important, which can provide reference information for bone disease. [3]
The expected benefit of bisphosphonates in improving bone mineral density is significant in women with breast cancer. Osteopenia and osteoporosis are common concomitant diseases at the time of cancer diagnosis, especially in postmenopausal women. In addition, adjuvant treatment with chemotherapy and / or aromatase inhibitors may lead to a further decrease in bone mineral density and an increased risk of bone fractures. Commonly used drugs include second generation bisphosphonates, aledronate and pamidronate, which have amino groups. Third generation bisphosphonates: risedronate and zoledronate, have a cyclic side chain, resulting in improved anti-resorptive properties. Although bisphosphonates have been used for over 100 years, they have only recently been established as first-line drugs in bone disease. [4,5]
Objective of the work
The aim of the study is to present a review of the literature on the effectiveness of bisphosphonates in patients with hormone-dependent breast cancers. The aim of our research is to describe BMD changes and fractures in patients with osteoporosis who have been treated with oral bisphosphonates, followed by serial tests of double energy X-ray absorptiometry (DXA) during drug interruption in clinical settings.

Material and methods
Bisphosphonates are pyrophosphate analogues that are commonly prescribed for the treatment of osteoporosis and other bone metabolic disorders. By inhibiting osteoclast function and survival, bisphosphonates reduce bone turnover, increase bone mineral density (BMD), and reduce the risk of osteoporotic fractures in patients with osteoporosis. Due to the excellent binding properties of hydroxyapatite and metallic surfaces and their good safety profile, bisphosphonates have been evaluated as formulating agents, especially for steric stabilization of nanoparticles. They exert their influence through several mechanisms, including direct inhibition of osteoclast precursor differentiation, osteoclast apoptosis and inhibition of the mevalonate pathway. [6]

Bisphosphonates are selectively captured by the bones and embedded in the sites of their active remodeling, and the remaining unbound portion of the drug is excreted unchanged by the kidneys. The amount of drug that will be associated with hydroxyapatite depends, among others, on the severity of bone turnover, route of administration, and the strength of the bisphosphonate interaction on the bone matrix. Activated osteoclasts cause degradation of the mineral on the bone surface and, as a consequence, release of matrix components, including bisphosphonates, which are then absorbed by osteoclasts. The accumulation of metabolic products of the phosphate analogues in osteoclasts induces cell apoptosis, which prevents further bone resorption. Newer generation substances also have, at least at the cellular level, a direct and indirect anti-tumor effect: inhibition of proliferation, adhesion, invasion and migration of cancer cells, inhibition of endothelial cell function (angiogenesis), activation of Tgd lymphocytes and modulation of macrophage and osteoblast activity. [7]
Bisphosphonates are classified based on whether or not they contain a nitrogen atom. Non-nitrogen-containing bisophonates such as etidronate and clodronate are less effective in inhibiting osteoclasts than nitrogen-containing bisophonates, i.e. pamidronate, aledronate, risedronate, ibandronate and zoledronic acid. The higher potency of bisphosphonates with a

nitrogen atom translates into greater efficacy in reducing the risk of skeletal complications in patients with multiple myeloma or metastatic breast cancer. Nitrogen-containing bisphosphonates exhibit anti-tumor activity by inhibiting cancer cell adhesion, migration, invasion and proliferation, and induce cancer cell apoptosis. These compounds act synergistically with chemotherapeutic agents. The greater potency of bisphosphonates with a nitrogen atom in conjunction with their direct antitumor, anti-angiogenic and immunomodulatory activity make these drugs theoretically more effective than clodronate when administered in supportive conditions. Bisophonates are mainly excreted intact by the kidneys and only a small amount is excreted through bile. Particular caution should be exercised when using bisphosphonates in patients with renal impairment. Bisphosphonates are well tolerated, usually without any serious side effects. Zoledronic acid and pimidronan often cause an acute phase reaction usually occurring within 3 days after the infusion, especially during the first few infusions. Fever, which occurs in about a third of patients, is the most common symptom, but muscle pain, joint pain, arthritis, joint swelling and headache may also occur. Hypocalcaemia is a known complication of all bisphosphonates. Corrected calcium and albumin levels should be monitored in patients treated with bisophonates, and daily calcium and vitamin D supplementation is recommended during treatment. Renal toxicity is more commonly associated with intravenous bisphosphonates.
Assessment of renal function before each infusion is required and treatment may be given with a dose adjustment. Gastrointestinal symptoms, usually mild, may occur, including nausea, vomiting, stomach ache and diarrhea. Unusual bone fractures have been reported rarely in patients receiving prolonged bisphosphonate therapy, these fractures often occur with minimal or no injury and heal slowly. If an atypical fracture occurs, bisphosphonate therapy should be discontinued. [8,9,10]

Evidence of BP efficacy in early stage breast cancer
Recently, a study was presented showing results (EBCTCG) where the results of an individual meta-analysis of patient data from 26 randomized studies assessing the role of adjuvant BP in early stage breast cancer. BP therapy was associated with a modest, but significant improvement in distant recurrence rates in the study population of over 18,700 patients (10-year gain of 1.4%; $p = 0.03$). However, in the postmenopausal subgroup (11,767 women) there was a significant 28% reduction in the risk of bone recurrence and an 18% reduction in the risk of death from breast cancer (10-year increase in mortality from breast cancer 3.3%; $p = 0.002$). As research into the effects of bisphosphonates in vitro and in vivo systems progresses, they have found clinical application both in the therapy of diseases with calcium metabolism disorder and in the diagnosis of diseases of bone and non-skeletal tissues, as well as in theoretical studies on regulatory mechanisms of calcium management. [11]
The biological activity of bisphosphonates can be modified by changing the structure of substituents (R1, R2) at the methylene carbon atom. The P-C-P fragment is responsible for binding to the bone mineral, and the binding is strengthened by introducing the hydroxyl group (-OH) in place of the R1 substituent. The spatial structure of the R2 side chain determines the cellular effect of bisphosphonates and their relative efficacy as bone resorption inhibitors. Each bisphosphonate has its own activity profile, determined by the individual properties of the side chain. [12]
The molecular mechanism of action of nitrogen-containing bisphosphonates. Unlike previous compounds, second and third generation bisphosphonates bind and inhibit farnesyl diphosphate synthase (FPP) activity, a key enzyme in the mevalon pathway, which is important in the production of cholesterol and other sterols, as well as isoprenoid lipids such as farnesyl diphosphate (FPP) and geranylgeranyl diphosphate GGPP). Inhibition of this enzyme occurs even at very low concentrations. These metabolites form the basis for the

synthesis of important compounds, e.g. dolichol or ubiquinone, and are necessary in the prenylation of proteins, including small GTPases. Prenylation is the transfer of an isoprene group from FPP or GGPP to the cysteine residue present in the modified protein in a specific recognizable motif at the C-terminus of the given protein. This modification is necessary due to the proper functioning of signals important for transduction in the GTPase cell. As a result of inhibition of FPP synthase, GTPases such as Ras, Rho, Rac, Cdc42 and Rab are not prenylated. The result is a disruption of the osteoclast cytoskeleton organization, actin ring formation, membrane folding, and cellular vesicle movement. As a consequence, this leads to a loss of osteoblast resorptive properties and ultimately to cell apoptosis. Since FPP is an enzyme commonly found in tissues, nitrogen bisphosphonates also have the ability to affect other types of cells. Their ability to inhibit the prenylation of Rap 1A has been demonstrated in cultures of all types of primary cells, as well as osteoclasts, osteoblasts, macrophages, epithelial cells as well as breast, prostate and myeloma cancer cells. Macrophages and osteoclasts appear to be most sensitive to low levels of nitrogen bisphosphonates in vitro. The sensitivity of various cells to nitrogen bisphosphonates most likely depends largely on their ability to absorb enough of these compounds to inhibit FPP synthase. Research suggests that FPP synthesis is the main focus of the pharmacological action of nitrogen bisphosphonates in osteoclasts in vivo. [13,14]

Other molecular mechanisms of bisphosphonate action. The next site of action of these compounds is the ATP-dependent proton pump located in the cell membrane of the folded osteoclast. Its role is to acidify the resorptive cavity necessary for the degradation of the bone matrix. In addition, bisphosphonates have the ability to directly inhibit several hydrolytic enzymes involved in osteoclast-dependent resorption. They also affect the activity of tyrosine phosphatases responsible for the formation and maturation of osteoclasts. [15]

Bisphosphonates are an important class of chemical compounds that have recently found application in the treatment of diseases associated with impaired calcium metabolism (Paget's disease, osteoporosis, myeloma, osteolysis associated with malignant hypercalcemia, bone metastases, primary hyperparathyroidism) and diseases with excessive deposition. calcium phosphate deposits (atherosclerosis, kidney stones, arthritis, calcification of artificial heart valves, periarticular and other heterotopic ossification). The main need for bisphosphonates is associated with the treatment of osteoporosis. Osteoporosis is a chronic, progressive disease characterized by low bone mass and degradation of bone tissue microarchitecture. It leads to a weakening of bone strength and, consequently, to an increased risk of fractures. Primary and secondary osteoporosis are distinguished. Primary osteoporosis includes idiopathic (including juvenile and adult 80%) and involutionary osteoporosis (type I postmenopausal osteoporosis and type II senile osteoporosis). Postmenopausal osteoporosis accounts for 80% of involutionary osteoporosis. Secondary osteoporosis includes osteoporosis accompanying or resulting from other disease states. These include posteroid osteoporosis, in hyperparathyroidism, caused by malabsorption syndrome, vitamin C and D deficiency, immobilization, chronic heparin treatment, and alcohol and nicotine abuse. The primary goal of osteoporosis treatment is to prevent fractures. So far, the effectiveness of therapy has been assessed on the basis of estimation of the risk factor for fractures, an increase in bone mineral density and the rate of bone remodeling. Activities in recent years have been supplemented with clinical trials. They showed the effect of bisphosphonates (alendronate) in reducing the incidence of spine, femoral and wrist fractures. It has been documented that bisphosphonates increase bone mass throughout the skeleton, especially in the spine and femoral neck, and reduce losses. [16,17]

The rich spectrum of action of older generation bisphosphonates (clodronate, etidronate) in the treatment of bone metabolism disorders and bone diseases should also be supplemented with anti-inflammatory effects in arthritis, manifested by a decrease in the level of

proinflammatory cytokinins. To date, over 10 different preparations have been developed. Currently, bisphosphonates are used in medical diagnostics (bone scintigraphy). Many cancers are osteoporotic or bone metastases, including breast, prostate, lung or kidney cancer. They are also like multiple myeloma, which mainly grow in the area of the bone marrow. Their growth often causes hypercalcemia, severe bone pain, destruction of their structure, resulting in pathological fractures. Studies show that the skeleton is the most common site for metastatic disease, and that at least 90% of patients with advanced cancer develop into bone lesions. The use of oral and intravenous bisphosphonate therapy in breast cancer resulted in significant relief of bone pain and reduction of skeletal complications. [17]

Conclusions

In Poland, around 15,000 osteoporosis patients suffer fractures of the proximal femoral base annually, about 20% of them die within six months of the fracture, the remainder mostly become invalids. Limiting fracture risk is therefore the primary goal of osteoporosis treatment. Bisphosphonates that inhibit bone resorption and increase its mass are now becoming one of the most important therapeutic groups in the prevention and treatment of this disease. New generations of effective bisphosphonates and progress in discovering the mechanisms of their action at the cellular and molecular level are constantly expanding the spectrum of the biological action of pharmacologically active bisphosphonates, including e.g. their anti-cancer, anti-inflammatory or cholesterol lowering activity due to blocking the mevalon pathway enzymes. At the same time, with an extended spectrum of activity, they do not show undesirable side effects, such as teratogenicity, mitogenicity and carcinogenicity. No interactions with other drugs have been described. It is possible that in the future bisphosphonates will be invented and synthesized, which will be characterized by a large difference between bone resorption inhibiting activity and their mineralization, with a simultaneous lack of increase in toxicity, increase in bioavailability, not causing gastric problems. Bisphosphonates may also in the future be used as carriers of drugs acting on the skeleton. [18,19]

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