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Significance of zoledronic acid in the adjuvant therapy in patients with breast cancer

Abstract

Introduction. Zoledronic acid is a medicine belonging to the bisphosphonate group. Its action is to inhibit the function of osteoclasts, which leads to a reduction in bone resorption. This preparation has a proven effect in the treatment of osteoporosis and Paget's disease. Bisphosphonates have also found use in the treatment of breast cancer. Studies conducted for many years indicate that zoledronic acid works most favorably in combination with adjuvant therapy. Breast cancer patients who are postmenopausal and being treated with chemotherapy are at risk of bone mass loss and hypercalcemia. Bisphosphonates effectively manage this. In addition, zoledronic acid indirectly exerts anticancer effects by modulating the immune system. All this allows us to conclude that taking this drug reduces the risk of bone metastasis in breast cancer patients. Dosage is also key in all this. There are several regimens offered to osteoporosis and breast cancer patients. So far, the following have been studied: conventional dosing (4 mg IV every 3-4 weeks), maintenance dosing (4 mg IV every 3-6 months) and metronomic dosing (1 mg IV weekly). It cannot be ruled out that each of these regimens may have a different antitumor effect. By reviewing scientific works, we aim to present the treatment options with zoledronic acid for breast cancer patients. We will describe the impact on their results depending on the dosage and we will present the other side of the coin, which are the side effects of taking this preparation.

Aim. This review provides an overview of the effects and impact of zoledronic acid in adjuvant therapy in patients with breast cancer.

Material and methods. The article presents the current state of knowledge on zoledronic acid as an adjuvant treatment option in breast cancer patients. It is a detailed literature review using Google Scholar, PubMed and Journal of Education Health and Sport platforms. Publications using the following key words were analyzed: bisphosphonates, zoledronic acid, osteoporosis, breast cancer, bone metastases.

Conclusion. Women diagnosed with breast cancer should be treated in a multidisciplinary manner. We treat early detected cancers to achieve complete remission. Long-term survival is our primary goal, and in pursuing it we should consider the potential impact of this treatment on the patient's skeletal system. Clinical studies allow us to conclude that there is a correlation between the initiation of antiresorptive therapy at an early stage of cancer and overall survival. Additionally, zoledronic acid significantly reduced the number of fractures. The collected data allow us to conclude that the addition of zoledronic acid to the established treatment regimens has a potentially positive effect on the group of postmenopausal patients undergoing tamoxifen treatment or with existing bone metastases.

Keywords: bisphosphonates, zoledronic acid, breast cancer, osteoporosis, bone metastases.

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INTRODUCTION

Breast cancer is the most common malignant tumor in women, with most cases originating in the epithelial tissue of the breast gland. The National Cancer Registry reports that more than 22,000 new cases of breast cancer will be diagnosed in women in 2020. Unfortunately, between 5 and 10% of these patients will have cancer at an advanced stage. Statistics show that it is the second – after lung cancer – factor in oncological deaths among women. Breast cancer produces no symptoms for a long time and is most often detected during prophylactic ultrasound or mammography [1]. This means that at the time of detection, metastases may already be present. It is crucial for physicians to emphasize imparting knowledge about the prevention of this cancer. The treatment of breast cancer is complex and reflective of both the mental and physical health of patients. The most important, often primary, step is surgical removal of the tumor, known as breast-sparing surgery or mastectomy. Radiation therapy is also indispensable alongside surgery. It is used in its pre-invasive form and in the palliative use of ionizing radiation to treat distant metastases. The doctor then decides on systemic treatments, which include chemotherapy,

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hormone therapy and immunotherapy. Breast cancer has a strong propensity to metastasize to the bone. It is estimated that about 75% of women with advanced breast cancer develop bone metastases. The consequence of these metastases is disrupted calcium-phosphate metabolism and the balance between resorption and bone formation. Due to osteoporotic changes, they are more likely to suffer from bone-related incidents. Pathological fractures, pressure on the spinal cord, hypercalcemia and the risk of orthopedic surgery are among the many limitations in the lives of breast cancer patients with bone metastases. Another aspect that is acute for the skeletal system is adjuvant therapy. Estrogen and/or progesterone receptor expression is found in about 70% of breast cancer cases. Women with this type of cancer most often receive anti-hormonal therapy to reduce the risk of recurrence [2]. The preparations taken are usually antiestrogens and aromatase inhibitors. Long-term treatment with these preparations results in decreased estrogen levels, which adversely affects bone metabolism [3]. A final debilitating factor is the numerous chemotherapy regimens that contribute to bone mass loss. For several years, a method recognized by oncologists in supplementary proceedings has been the prophylactic administration of bisphosphonates. Bisphosphonates are drugs that inhibit the activity of osteoclasts, and thus are inhibitors of bone resorption. A unique example of bisphosphonates is zoledronic acid. It has been shown to be effective in preventing bone mass loss induced by cancer treatment. In addition, an indirect anticancer role of the acid, such as inhibition of angiogenesis, and a direct one, which are inhibition of proliferation, adhesion, and invasion of tumor cells, have been documented [4]. Many factors affect the effectiveness of zoledronic acid treatment. Prominent among them are the type of cancer, diagnosis before or after menopause, use of hormone therapy and the presence of bone metastases. Studies show that among all women with breast cancer, zoledronic acid is the most effective for patients with bone metastases [5].

MATERIAL AND METHODS

To describe reports on zoledronic acid and its importance in adjuvant therapy in patients with breast cancer, we searched the literature using the PubMed platform and Google Scholar. Our preferences in selecting review papers were the ones written in English and publications after 2000, cited by the American and European Societies of Clinical Oncology. The key words we used were bisphosphonates, zoledronic acid, osteoporosis, breast cancer, bone metastases.

Description of the State of Knowledge

Pharmacokinetics and mechanism of action of zoledronic acid

Zoledronic acid belongs to the 3rd generation of bisphosphonates and contains nitrogen in its composition. Its mechanism of action is based on its remarkably high affinity for hydroxyapatite crystals. After administration, it is selectively taken up by bone cells and is then incorporated into sites of active remodeling. Its antiresorptive action involves inhibition of the mevalonate pathway, which ultimately results in inhibition of bone resorption. The final process is the induction of osteoclast apoptosis. Treatment with zoledronic acid is safe because the drug is mostly bound to bone tissue, and its slow release into the systemic circulation results in long-lasting, low plasma concentrations of the agent. Zoledronic acid is not metabolized systemically. The unbound portion of the drug is excreted unchanged by the kidneys [4,6]. Zoledronic acid has a limited ability to penetrate the cell membrane, making its intracellular concentration in most types of cells very low. The exceptions are cells capable of pinocytosis, such as osteoclasts, monocytes, and macrophages. The ability of the drug to accumulate in the cells of the immune system and affect their metabolism may be another argument in favor of its anticancer effect [7].

Finally, in an experiment on mice treated with zoledronic acid, inhibition of angiogenesis was observed. The drug decreases the level of vascular endothelial growth factor (VEGF), and consequently reduces vascular endothelial proliferation [8]. In addition, a 2019 study revealed that zoledronic acid inhibits the expansion and immunosuppression of regulatory T cells. This is associated with slowing down the migration of tumor cells by blocking the RANK/RANKL pathway induced by Tregs [9]. Several studies have also noted that the combination of zoledronic acid with chemotherapeutic agents and hormonal treatment has synergistic effects [10].

Early stages of breast cancer and the adjuvant therapy with zoledronic acid

In the current era of prevention and women's awareness of self-examination, a significant percentage of breast cancers are detected at an early stage. These are cancers in- situ, or with metastasis confined to local lymph nodes. Patients diagnosed with premenopausal breast cancer and that have been put on first-line treatment must face the consequences of this treatment. Many chemotherapy regimens lead to inhibition of ovarian function and thus premature menopause. The consequence of this hormonal suppression is accelerated bone mass loss, which can even lead to clinical osteoporosis. Effective treatment would be hormone replacement therapy, which is used for natural or surgical menopause. However, a large group of patients have a hormone-dependent type of cancer, which means that hormones stimulate the division of cancer cells. For this reason, this form of treatment is contraindicated [11]. In addition, studies of adjuvant treatment with the luteinizing hormone-releasing hormone (LHRH) agonist goserelin, which is commonly administered to premenopausal women with cancer, show that circulating estrogen levels in the bloodstream drop to postmenopausal levels during therapy [12]. For this reason, bisphosphonates are particularly recommended for women with low estrogen levels caused by adjuvant therapy and chemotherapy [13,14]. The situation is different in the case of women who started anticancer therapy after menopause. Estrogen levels decrease during perimenopause and stabilize 2-3 years after menopause [12]. Drugs with proven effectiveness, commonly used among postmenopausal patients, are aromatase inhibitors. Taking these medicines results in reducing estrogen levels to even lower than during the natural menopause process. This is another key factor in the increased rate of osteolysis.

Antiresorptive agents, including zoledronic acid, prevent bone disorders. Its purpose is also to reduce bone pain in women (pre- and postmenopausal) with early stages of breast cancer [15]. Therefore, in many European countries zoledronic acid is listed in the guidelines as recommended for adjuvant treatment of breast cancer patients, however, in Poland it is issued under the off-label procedure.

Usage of zoledronic acid in advanced breast cancer with bone metastases

Breast cancer metastases are most often localized in the bones. Their occurrence indicates the advancement of the disease. Statistics say that about 75% of women with advanced breast cancer develop bone metastases. Patients at such a stage receive palliative treatment to alleviate symptoms from the skeletal system. The mechanism of the formation of cancerous processes within the bones involves continuous reconstruction. This process consists of resorption, for which osteoclasts are responsible, and repair with the participation of osteoblasts. Osteoblasts, by activating the resorption process, stimulate osteoclasts to destroy bone cells. Once the process is complete, osteoclasts undergo necrosis, and osteoblasts line the resorption cavity, creating an osteoid matrix there [16]. Bone turnover markers represent the continuous process of bone formation and resorption occurring in the bones. The variability of bone mass depends on this process. Zoledronic acid normalizes bone turnover. It has been shown that women with advanced breast cancer, who took zoledronic acid (which has normalized bone turnover), had a longer period free of bone events and a higher percentage of overall survival, compared to women who did not take it. Another action of this product is the documented inhibition of tumor cell adhesion to the bone matrix and the inhibition of the secretion of IL-6 produced by the stroma. Therefore, it has anti-inflammatory effects, and by inhibiting the mevalonate pathway it also reduces cholesterol levels [17]. In addition, there is an increasing amount of research on the effect of zoledronic acid on the survival of disseminated cancer cells. Research suggests that taking acid combined with adjuvant therapy and after chemotherapy alone reduces the number of disseminated cancer cells [18]. Taking all these arguments into account, we believe that taking zoledronic acid in advanced stages of breast cancer has a positive impact on the health and functioning of patients. First, it affects their lives' comfort by reducing the number of bone incidents, e.g. fractures, vertebral subluxations, and pressure on the spinal cord.

Dosage

The dosage of zoledronic acid depends on many factors. There are several clinically studied dosing regimens. The most common regimen in postmenopausal women with breast cancer in adjuvant therapy is intravenous administration of 4mg i.v. every 6 months for 3-5 years. In cases of metastasis, the frequency of the drug is increased to 4mg i.v. every 3 months for 2 years or 4mg i.v. every 3-4 weeks [19,20]. Monthly administration of zoledronic acid in patients with breast cancer metastases reduces the risk of bone complications and helps achieve therapeutic goals, i.e. improving clinical outcomes. However, the correlation between the dose and the anticancer effect of zoledronic acid should be more extensively investigated. During the literature review, we repeatedly came across an important factor that may be useful in assessing the effectiveness of zoledronic acid treatment. It is the level of vascular endothelial growth factor (VEGF) circulating in the blood. Its increased level may suggest a bad prognosis for the patient and herald deterioration of clinical results [19]. For patients facing the choice of treatment with zoledronic acid, it is crucial that it prolongs DFS, the time after completion of primary cancer treatment in which the patient has no signs and symptoms of that cancer. According to numerous studies, adding zoledronic acid to adjuvant therapy improves DFS in women with and without positive lymph nodes. In addition, randomized trials from 2017 show that a minority of patients experienced disease recurrence with distant metastases [19,20]. The third regimen is the metronomic dosing method, which involves low doses of zoledronic acid administered weekly. In 2011, a study was conducted comparing the classical administration of 4mg of acid 4 weeks apart with 1mg weekly for 4 weeks and evaluated the effect of both regimens on angiogenesis. There was a much greater decrease in serum VEGF levels in patients taking acid weekly. This study sheds new light on the metronomic regimen. Indeed, it suggests an advantage of using low doses over conventional dosing [21]. In summary, studies to date have not determined which dosing regimen is the best. The 4-week intervals have been determined empirically. Most publications have found no significant differences in the efficacy or toxicity of therapy [22]. During all types of bisphosphonates, vitamin D3 and calcium supplementation should be remembered. Ultimately, this is a drug administered intravenously, so the patient should be adequately hydrated before its administration.

Contraindications

The drug should not be used in case of hypersensitivity to any active substance, including other bisphosphonates. There are insufficient data on the use of zoledronic acid in pregnant women. Reproductive toxicity has been demonstrated in animal studies. The potential risk to humans is unknown. Pregnancy and lactation are therefore contraindications to zoledronic acid use. However, with chemotherapy and complementary treatment, the risk of pregnancy is low. Another limiting factor in the use of zoledronic acid is impaired renal function. The dosage of the drug should depend on creatinine clearance [23].

Side effects

The most common side effects of zoledronic acid include bone, muscle and joint pain, generalized pain, fatigue, morning stiffness, nausea and constipation. Patients often complain of flu-like symptoms such as fever or chills. In laboratory tests and morphology, the most common abnormalities are anemia, hypophosphatemia, and hypocalcemia [24]. Rare but serious adverse events include osteonecrosis of the jawbone and necrosis of the external auditory canal. The risk of osteonecrosis of the jawbone increases with long-term treatment in women with advanced breast cancer with bone metastases. Patient education regarding dental visits is essential. Once you start taking the medication, a dental checkup is recommended every 4 months. It is also important to remember to maintain oral hygiene [25]. There are many reports of local infections in breast cancer patients after tooth extraction or other invasive dental procedures. The consequence of a developed infection can even be osteomyelitis. Most patients report mild side effects. Osteonecrosis of the jawbone is exceedingly rare and is estimated to occur in less than 0.5% of cases. The last significant limitation to the use of zoledronic acid is impaired renal function. Before initiating therapy, it is recommended to examine their functional activity [26]. As renal failure develops, the risk of hypocalcemia and increased concentration of parathyroid hormone in the blood increases. Therefore, calcium levels should be regularly monitored in these patients and calcium and vitamin D supplementation should be recommended [23].

DISCUSSION

We have covered many topics regarding zoledronic acid in this review. Starting from the pharmacokinetics of the drug and ending with side effects. We have repeatedly emphasized the benefits of adding bisphosphonates to complementary treatment of breast cancer. Are there any negative opinions regarding treatment with zoledronic acid as an adjuvant therapy? Zoledronic acid has proven its positive effect in many studies by protecting against fractures and extending the period of remission. The argument for introducing zoledronic acid into treatment should be its anticancer effect, demonstrated in in vitro and in vivo studies. These actions include inhibition of angiogenesis, suppression of local inflammation, prevention of bone adhesion and induction of apoptosis of cancer cells. Taking all these factors into account, it can be assumed that the benefits outweigh the side effects of the drug. Therefore, the use of zoledronic acid in the adjuvant treatment of breast cancer is justified [27]. The impact of hormone therapy on the microenvironment of the bone also plays a fundamental role in determining who may benefit most from treatment with zoledronic acid [28]. Interestingly, the antimetastatic effect of zoledronic acid in the adjuvant therapy of postmenopausal women with breast cancer is limited only to breast cancer. No benefit from taking this drug has been observed in postmenopausal patients with lung cancer or in men after chemical or physical castration due to prostate cancer [29]. With all its advantages, one should not forget about the potential harm that zoledronic acid can cause. Clinical oncologists should not ignore the complaints reported by patients. Any side effects should be taken seriously. One meta-analysis describes a phenomenon called acute phase reaction (APR). The risk of its occurrence is the highest during the first intravenous infusion of zoledronic acid. Younger women have a greater predisposition to APR. This is in contrast to older women and those who previously used oral bisphosphonates [30].

In addition, an important aspect of zoledronic acid treatment is the control of renal and parathyroid function. Elderly patients with impaired renal excretory function prior to zoledronic acid therapy may develop advanced renal failure during its use. Intravenous administration of this potent bisphosphonate, which is zoledronic acid, can result in hypocalcemia, which will eventually lead to secondary hyperparathyroidism. Most deviations in serum parathyroid hormone concentration are mild, and after completion of therapy, its level returns to normal. It has been recognized that PTH levels can affect the occurrence of serious side effects, such as osteonecrosis of the jawbone. In addition, it was found that patients with higher serum PTH levels had a worse prognosis. Finally, there was no confirmation whether persistently elevated PTH levels in patients with bone metastases reveal a worse clinical condition regardless of therapy [31]. However, it is worth considering each pros and cons before starting zoledronic acid therapy. It is crucial that patients be thoroughly informed of the possible benefits and side effects associated with this treatment. Each decision should be conscious and described in the medical record maintained by the physician.

CONCLUSION

In summary, bisphosphonates, and zoledronic acid in particular, have become an indispensable part of breast cancer care. Studies comparing the effects of other bisphosphonates with zoledronic acid clearly show that zoledronic acid is most effective in dealing with skeletal events caused by chemotherapy and hormone therapy in early-stage breast cancer. It also effectively eliminates bone pain associated with cancer metastasis to the bone. Additionally, it has multi-faceted anti-cancer effects, inhibiting the development of metastasis. Like most preparations, treating one ailment may cause harm elsewhere. Therefore, it is worth warning patients about the side effects of this treatment. One of the most serious is osteonecrosis of the jawbone. It is a rare complication, but often the most common reason for abandoning therapy. Analyzing the above information, we conclude that the gains a patient may have from taking zoledronic acid significantly outweigh the losses.

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