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SOME CLINICAL ASPECTS OF ANTIRESORPTIVE TREATMENT IN PATIENTS WITH BONE METASTASES

Complications associated with bone metastasis and bone involvement in multiple myeloma include pain, disability, loss of self-care abilities, and a decline in quality of life, often requiring the use of narcotic analgesics. The use of bone-modifying agents (BMAs) helps to delay or avoid the development of bone complications.

All practical recommendations are consistent with each other and follow a single strategy for administering antiresorptive therapy (ART) to patients with bone metastases. Despite this, there are several practical issues that are of particular interest to clinicians: 1) the choice of drugs for ART in patients with various types of tumors and bone metastases; 2) schemes and regimens for the safe use of BMAs, and the prevention of adverse events during long-term treatment. The review article discusses some aspects of the use of ART to preserve bone microarchitecture and reduce the risk of fractures in patients with bone metastases. The authors conclude that there is currently no alternative to ART for the prevention of bone complications and the management of pain.

Keywords: antiresorptive therapy, bone-modifying agents, bone metastases.

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Introduction. Modern antiresorptive therapy (ART) is aimed at reducing bone loss, preserving bone microarchitecture, and decreasing fracture risk. The key to preventing bone loss is the suppression of osteoclast function — multinucleated giant cells responsible for bone tissue resorption. Osteoclasts initiate physiological bone remodeling during growth, tooth eruption, and fracture healing [30]. However, they can also cause bone loss in pathological conditions such as bone metastases [23].

Bisphosphonates, synthetic analogues of pyrophosphates that naturally occur in the bone matrix, are among the most widely used agents for suppressing osteoclast activity [9, 25, 26, 31]. In bisphosphonates, an oxygen atom is replaced by a carbon atom, which makes the molecule more stable. The mechanism of action of bisphosphonates (alendronic, zoledronic, risedronic, and ibandronic acids) is not fully understood. It is believed that during bone resorption, the osteoclast — while removing bone tissue — takes up the bisphosphonate, most likely along with calcium and the bone

matrix [32]. Consequently, the alteration of signaling proteins crucial for osteoclast activity is halted, potentially inducing apoptosis in the bone-resorbing cell [11].

Within this class of compounds, zoledronic acid (ZA), a nitrogen-containing bisphosphonate, demonstrates the highest activity [29]. ZA has a high affinity for bone because it binds to hydroxyapatite in bone tissue through Ca^{2+} chelation [10, 28]. After being taken up by bone-resorbing osteoclasts, ZA can induce osteoclast apoptosis by inhibiting the mevalonate pathway mediated by farnesyl pyrophosphate synthase (FPPS), as well as through the activation of reactive oxygen species (the ROS-induced pathway) [33]. In addition, ZA can suppress the differentiation of macrophages into osteoclasts. It also reduces the expression of the receptor activator of nuclear factor- κB ligand (RANKL), thereby diminishing the interaction between RANKL and RANK. The results are in a reduced number of osteoclasts and a subsequent decrease in bone resorption and tumor-related bone destruction. ZA can also influence non-canonical Wnt signaling by lowering the levels of the signaling proteins Wnt5a and CaMKII (Ca^{2+} /calmodulin-dependent protein kinase II). It markedly decreases intracellular Ca^{2+} , suppresses the expression of calmodulin and CaMKII, and ultimately inhibits osteoclast differentiation. ZA exerts multifaceted antitumor effects by inhibiting proliferation, survival, migration, invasion, and angiogenesis of cancer cells, inducing apoptosis, counteracting chemoresistance, stimulating

immunity, and synergizing with other anticancer therapies.

Denosumab [19] is another agent that suppresses bone resorption. It is a fully human recombinant monoclonal IgG2 antibody against RANKL, a cytokine that plays a key role in osteoclast activation [27]. By blocking RANKL, denosumab inhibits osteoclast formation, function, and survival, thereby reducing the intensity of bone resorption. Thus, denosumab exhibits antiresorptive activity. Recent studies have shown that denosumab may also modulate the antitumor immune response by enhancing the activity of cytotoxic T-lymphocytes [16]. Comparative studies have demonstrated that denosumab is more effective than bisphosphonates in slowing the development of skeletal-related complications [13, 18]. Denosumab reduces osteoclast formation without impairing the function of mature cells. As a biologic agent, denosumab does not accumulate in bone tissue and does not exert delayed effects, with its impact fully reversible upon treatment discontinuation [8].

The prevention of skeletal complications is especially important in patients with bone metastases from malignant tumors. Such complications are often associated with pain, functional disability, loss of independence in daily activities, and a decline in quality of life, frequently requiring the use of opioid analgesics. Studies indicate that 65–75% of patients with bone metastases experience pain, impaired mobility, and reduced physical function [21].

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Early initiation of bone-modifying agents (BMAs) can delay or even prevent the onset of skeletal complications. Evidence suggests that BMA therapy reduces the incidence of such complications by 41–54% [12], thereby improving five-year survival in cancer patients and lowering the additional healthcare costs associated with managing these events. Consequently, antiresorptive agents have become an essential component of supportive care for oncology patients with bone metastases or bone involvement in multiple myeloma.

In Russian Federation, physicians can follow the practical guidelines of the Russian Society of Clinical Oncology (RUSSCO) for supportive therapy in “Bone Tissue Pathology” [6], which are updated annually in accordance with new scientific evidence and international approaches to patient management. In other countries, practical guidelines are developed by organizations such as NCCN, ESMO, ASCO, and others. All these guidelines are largely consistent with one another and follow a unified strategy for prescribing ART to patients with bone metastases. Nevertheless, several practical issues remain of particular interest to clinicians. Key among these are: 1) the selection of agents for ART in patients with different tumor types and bone metastases; and 2) the regimens and schedules for the safe use of BMAs, including the prevention of adverse events during long-term treatment.

The use of BMAs for specific disease entities is outlined in the clinical guidelines of the Russian Ministry of Health for the management of patients with breast cancer [3], prostate cancer [4], and lung cancer [2]. In addition, a guideline entitled “Metastatic Bone Disease in Malignant Tumors” has been developed and is available on the websites of the Russian Society of Clinical Oncology and the Association of Oncologists of Russia [22]. BMAs are an effective component of supportive therapy and should be administered alongside primary cancer treatment. Their effectiveness in preventing skeletal complications has been consistently demonstrated in numerous clinical studies [1, 5, 7, 21].

Antiresorptive therapy for tumors with bone metastases. This section focuses on selected aspects of ART use in solid tumors with a high incidence of bone metastases. There are certain discrepancies in the approaches to ART in prostate cancer (PC). According to the general description of the drug denosumab 120 mg, its administration is recommended for patients with solid tumors

in the presence of bone metastases. In other words, the presence of metastases, regardless of their characteristics, may be an indication for prescribing BMAs. However, according to all clinical guidelines, ART is prescribed only upon the development of castration resistance. Data from randomized clinical trials indicate that adding zoledronate to first-line long-term hormonal therapy (STAMPEDE trial) in patients with endocrine-sensitive prostate cancer (ESPC) did not show any signs of improved survival. Moreover, in the CALGB 90202 study, comparing zoledronate and placebo in ESPC with bone involvement as the primary endpoint, early treatment with zoledronate did not lead to a significant reduction in the incidence of skeletal events. Similar studies have not been conducted to assess the efficacy of denosumab 120 mg. Nevertheless, a beneficial effect of bone-modifying agents in reducing pain in these patients cannot be excluded. In randomized clinical trials comparing denosumab and zoledronate in men with bone metastases from castration-resistant prostate cancer, denosumab delayed the time to the first skeletal-related event and reduced the overall incidence of skeletal complications by 18% compared to zoledronate [17].

In contrast to prostate cancer, there is no controversy over administering BMAs to all patients with bone metastases from breast cancer. Randomized clinical trials have shown that in these patients, denosumab was statistically superior to zoledronate in delaying both the first and subsequent skeletal-related events, as well as in slowing the progression of bone pain [15].

ART is recommended for patients with breast cancer and castration-resistant prostate cancer who have bone metastases, regardless of the presence of clinical symptoms. For other solid tumors, therapy with bone-modifying agents is advised when the expected survival is ≥ 3 months or if the symptoms are clinically significant [12].

Over the past decades, the use of BMAs for the treatment of patients with metastatic malignancies has increased. The patients with oligometastatic disease may survive more than 10 years after diagnosis. As life expectancy has increased, it has become important to assess the cumulative risks of long-term use of bone-modifying agents, the incidence of adverse events, and the frequency of drug administration [12].

Regimens and protocols for the safe use of bone-modifying agents. The choice of ART administration sched-

ule is of critical importance. Randomized clinical trials in patients with breast cancer, castration-resistant prostate cancer, or multiple myeloma demonstrated comparable efficacy in preventing skeletal complications when zoledronate was administered every 12 weeks versus every 4 weeks. However, a greater number of patients receiving zoledronate every 12 weeks required surgical intervention on bones [20]. Considering that the follow-up period was relatively short and the results suggested a potential increase in serious skeletal events with less frequent dosing, a 4-weekly administration schedule is considered appropriate during the first 3–6 months of treatment [12]. Based on pharmacokinetics, treatment interruptions with denosumab are not recommended [14]. Denosumab 120 mg should be administered once every 28 days for an extended period, until otherwise indicated. Unlike bisphosphonates, denosumab does not integrate into the bone matrix. This drug can be regarded as “heavy artillery,” providing faster and more effective suppression of bone resorption compared with zoledronic acid, thereby helping to prevent disabling complications. Maximum benefit from denosumab is observed in patients with active malignancy, multiple metastases localized in the axial skeleton, and at risk of pathological fractures. If denosumab is discontinued for more than 6 months, a single dose of zoledronic acid is recommended to suppress rebound osteolysis [6].

In most cases, therapy with osteomodifying agents (OMAs) is initiated upon detection of bone metastases and continued throughout the course of cancer treatment. Therefore, the safety profile of OMAs and the incidence of adverse events are of particular importance. Among these, osteonecrosis of the jaw (ONJ) and atypical fractures are the most clinically significant. ONJ occurs more frequently with intravenous administration of OMAs and is influenced by both dose and dosing frequency. Monthly administration of bisphosphonates or denosumab is associated with a higher risk of ONJ compared to oral bisphosphonates or administration of zoledronate or denosumab 60 mg every six months for bone loss prevention. The risk may be somewhat higher in patients with multiple metastases compared to those with solid tumors and can be further increased when OMAs are combined with antiangiogenic agents or corticosteroids [6]. With monthly treatment, the incidence of ONJ for both zoledronate and denosumab is approximately 1% per year [12]; however,

some studies suggest that this rate for denosumab may be substantially underestimated [24].

Another serious adverse effect associated with the use of BMAs is atypical femoral fractures in the subtrochanteric region and femoral shaft in patients. Radiographic studies of fractures indicate a link between femoral fractures and the use of bisphosphonates, which tend to accumulate in areas where stress fractures develop, while suppression of intracortical remodeling at fracture sites may impair healing processes. The absolute risk of fractures in patients receiving bisphosphonates or denosumab is low, ranging from 3.2 to 50 cases per 100,000 person-years. The risk is higher with long-term use of BMAs (on average 7 years) and may decrease after discontinuation of therapy [12].

It should be noted that most clinical questions regarding the use of antiresorptive drugs are addressed in the supportive care guidelines available on the RUSSCO website [6]. Bone-modifying agents are compatible with all existing anticancer drugs and radiation therapy methods, and their administration is not a contraindication for surgical treatment.

Conclusion. Antiresorptive agents are an essential component of supportive therapy for oncology patients with bone metastases and bone involvement in multiple myeloma. To date, there is no alternative to ART for preventing skeletal complications and managing pain in these patients. This is supported by numerous clinical studies.

The authors declare no conflict of interest.

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