Western European Journal of Medicine and Medical Science
Volume 2, Issue 11, November 2024
https://westerneuropeanstudies.com/index.php/3
ISSN (E): 2942-1918 Open Access| Peer Reviewed

EVALUATION OF THE EFFECTIVENESS OF DENOSUMAB IN BONE METASTASES OF BREAST CANCER

Khakimov G.A[1], Atakhanova N.E[2] , Khakimova G.G[3] , Almuradov A[4]., Almuradova D.M[2]., Ziyayev Sh.V[1]., Ismailov J.Kh[2].,
Republican specialized scientific and practical medical center
Oncology and Radiology Tashkent city branch[1]
Tashkent Medical Academy[2]
Tashkent Pediatric Medical Institute [3]
Tashkent State Economic Institute[4]

Summary . Breast cancer is a heterogeneous disease, the pathogenesis of which is determined by the complex interaction of hormonal, metabolic, exogenous and other factors and is the most common malignant neoplasm among women in the world. According to various authors, breast cancer is characterized as a tumor that often metastasizes to the bones (from 13.5 to 85%), and in terms of the frequency of localization of metastatic lesions, the skeleton ranks third after the lungs and liver. Metastatic bone damage in breast cancer is an urgent problem. Most patients are indicated for osteomodifying therapy. The article defines a portrait of a patient for whom the use of antiresorptive drugs can be postponed or canceled. The results of the registration study showed that denosumab is not only not inferior in effectiveness to zoledronic acid, but also reduces the risk of development and significantly delays the onset of the first and subsequent skeletal complications, including the need for radiation therapy, the development of hypercalcemia and pathological fractures. Denosumab is an effective, well-tolerated drug that increases the chance of preventing RCM in breast cancer.

Key words: bone metastases, osteomodifying agents, antiresorptive therapy, bisphosphonates , zoledronic acid, denosumab

Relevance. Metastatic bone lesions in breast cancer remain a pressing problem despite progress in the early diagnosis of this disease and the success of antitumor drug treatment. The frequency of metastatic skeletal lesions in breast cancer (BC) is, according to various sources, 65–75%, slightly “second” only to prostate cancer and multiple myeloma [1,10]. Treatment options for patients with bone metastases have expanded significantly in recent decades due to the introduction into clinical practice of drugs that inhibit bone resorption— osteomodifying agents (OMAs). It was OMA that came to the fore in the palliative treatment of these patients, replacing external irradiation, which had been used for analgesic purposes for a long time , as well as to prevent bone fractures [2,15]. Bisphosphonates are a group of drugs that are analogues of bone matrix pyrophosphate , dating back to the creation of clodronate in 1992. Its use in breast cancer has significantly reduced the incidence of skeletal events. Subsequent generations of drugs in this group showed increasing effectiveness: in 1996 pamidronate came to the clinic , in 2002–2003 - ibandronate and, finally, zoledronate , which was the most active bisphosphonate and firmly took a position in clinical recommendations for accompanying therapy in the presence of metastases in the patient bone tissue of any solid tumors. In 2010, new opportunities opened up in this area: the first and so far only targeted drug affecting bone resorption, denosumab , appeared . To understand the mechanism of action of OMA, it is necessary to recall the existence of the so-called vicious circle of bone destruction. Tumor cells enter the bone through the hematogenous route. When in the bone microenvironment, they

Western European Journal of Medicine and Medical Science
Volume 2, Issue 11, November 2024
https://westerneuropeanstudies.com/index.php/3
ISSN (E): 2942-1918 Open Access| Peer Reviewed

produce cytokines and growth factors that stimulate osteoblasts to produce a special protein, RANK-L (receptor activator of nuclear factor kappa B ligand). The connection of the RANK ligand with the RANK receptors on the surface of young osteoclasts triggers their maturation, their activation occurs, and bone tissue resorption begins. At the same time, during the process of bone resorption, other biologically active substances are released. active substances (growth factors: platelet , insulin-like, prochondrogenic , epidermal , etc.), which stimulate the proliferation of the tumor cells themselves. This maintains the vicious circle of bone resorption. Bisphosphonates disrupt the metabolism of osteoclasts, the adhesion of tumor cells to the bone matrix, suppressing their migration, invasion and angiogenesis , and also activate the natural death of osteoclasts - apoptosis . Denosumab , being an antibody, binds the RANK ligand , thereby preventing the maturation of osteoclasts and reduces their number without being incorporated into the bone matrix [11,12].

As is known, breast cancer is a tumor sensitive to drug treatment. The disease more often affects older age groups of women. The overwhelming majority of breast cancer cases by molecular subtype are luminal cancer. Knowing about the high effectiveness of hormone therapy, with a low risk of bone complications, it is possible to postpone the appointment of OMA in such patients. Metastases in bone tissue in breast cancer, as a rule, are mixed, that is, they contain both lytic and blastic areas. For the clinician, it is important not so much to determine the type of metastasis as their localization in the skeleton. Favorite bones for metastasis are the spinal column (especially the thoracic and lumbar regions), pelvic bones; less often - ribs, tubular bones, cranial vault; extremely rarely - small bones of the limbs, facial skeleton [14]. Thus, if a patient has metastases in the bones of the supporting skeleton, there is no point in postponing antiresorptive therapy. Lesions located in, say, the ribs or skull bones, especially if they are few in number, can be observed [6,13].

When prescribing OMA, it is recommended to carry out sanitation of the oral cavity and inform the patient about the need to maintain oral health; however, it is very problematic for the oncologist to monitor the implementation of these recommendations in real practice. Thus, a patient with dental pathology, say, teeth with a poor prognosis, poorly controlled dental structures, as well as a patient planning dental prosthetics in the near future, is clearly not a candidate for treatment with denosumab or zoledronic acid [8,9]. You can resort to this treatment only after making sure that your teeth and gums are in satisfactory condition. A special category of patients is represented by patients with the presence of both bone metastases and multiple visceral metastases. Clinical practice shows that it is the dissemination of the tumor to the liver, lungs and other organs (often the brain) that determines the patient's prognosis. In the absence of pain and a low risk of skeletal complications, the prescription of antiresorptive therapy in such cases seems inappropriate, since the process of bone remodeling is not rapid and usually takes from several months to 1 year. Therefore, it is important to assess life expectancy: if it is less than 3 months, osteotropic therapy is not indicated [3,5,6,7].

The purpose of our study is to evaluate the activity of Denosumab compared to Zolendra acid in patients with breast cancer metastases in the skeletal bones.

Materials methods. To solve the research problems, we analyzed the data of 76 patients with breast cancer who received treatment at the Republican Specialized Scientific and Practical Medical Center of Oncology and Radiology of the Tashkent City Branch from 2019 to 2021. The drug Denosumab was prescribed as a subcutaneous injection of 120 mcg compared with intravenous administration of 4 mg. Zoledric acid every 4 weeks for week 120. The effectiveness criteria were the time until the development of an unfavorable outcome from the

Western European Journal of Medicine and Medical Science
Volume 2, Issue 11, November 2024
https://westerneuropeanstudies.com/index.php/3
ISSN (E): 2942-1918 Open Access| Peer Reviewed

skeleton (pathological fractures, radiation therapy to bone for any reason, hypercalcemia), the number of patients with skeletal events and their frequency, and the dynamics of pain. 14 days after completion of the 6th and 12th courses of chemotherapy, scintigraphy of skeletal bones was performed to determine metastatic foci in the bones. The rate of immediate antitumor response was assessed according to RECIST criteria. The selection of the main characteristics and statistical criteria for their comparison was carried out after studying the distribution of the characteristic and comparing it with the Gaussian distribution using the Kolmogorov-Smirnov criterion. For numerical characteristics with a distribution corresponding to the Gaussian distribution, the average values of numerical characteristics and the standard error of the mean were calculated. The significance of differences P was calculated by discriminant analysis. If the number of groups was more than two, P was calculated taking into account multiple comparisons (according to the Scheffe test). For traits with a distribution significantly different from normal, the median, quartiles were calculated, and nonparametric methods for comparing unrelated traits were used (Kruskal-Wallis Anova & Mediantest when the number of groups being compared is more than two and Mann-Whitney when comparing two groups). When comparing frequencies, contingency tables of characteristics were constructed. To calculate P, Fisher's exact test (for small group sizes) and the nonparametric ci-2 test were used.

Results. Use of denosumab increased the time to the onset of an adverse skeletal outcome (619 days vs. 376 days, p = 0.32). Number of patients with unfavorable skeletal outcome in the denosumab group was 11.8% compared with 29.4% in the group receiving zoledronic acid (p = 0.23). The incidence of adverse skeletal outcomes was 0.16 versus 0.65 outcomes per patient per year (p = 0.13). By the ninth month, pain decreased by 62 and 42%, respectively (p = 0.31). The median time to the onset/increase of pain in patients with an initial pain level of 0–4 points was significantly longer in the denosumab therapy group – 32.4 months versus 25.1 months in the zoledronic acid therapy group (HR = 0.78; 95% CI 0.67–0.92; p = 0.0024). Median time to development of moderate or severe pain syndrome (Worst scale) Pain Score > 4) in patients receiving denosumab therapy was almost a month longer compared with the zoledronic acid therapy group (88 and 64 days, respectively) (HR = 0.87; 95% CI 0.79–0.97; p = 0.009). ECOG status was maintained unchanged throughout the study in 59% of patients receiving denosumab and 55% in the zoledronate group . Worsening ECOG status was observed in 36% in the denosumab group and 41% in the zoledronic acid group [19]. According to the requirements of the instructions for the use of zoledronic acid, the dose of the drug was reduced in 13% of cases, the administration of the drug was temporarily stopped due to an increase in creatinine levels in 56%. Denosumab never required dose adjustments or delays due to renal toxicity. Overall, the incidence of adverse events associated with renal toxicity was significantly lower in the denosumab group (4.9% vs. 8.5%; p = 0.001). Acute infusion reactions with influenza-like syndrome during the first 3 days after drug administration (hyperthermia, weakness, bone pain, arthralgia) were significantly more often observed in the zoledronic acid group (27.3%) compared to the denosumab therapy group (10.4%) (p < 0.0001). Denosumab was generally well tolerated . The incidence of osteonecrosis of the jaw was 2.0 and 1.4% in the denosumab and zoledronic acid groups, respectively. Infusion-related reactions as well as renal toxicity were much less common in the denosumab group , while hypocalcemia was slightly more common in patients treated with denosumab compared with zoledronic acid (5.5% and 3.4%, respectively).

Conclusions. With the advent of bisphosphonates , the situation when almost every patient with bone metastases from breast cancer had a pathological fracture and required radiation

Western European Journal of Medicine and Medical Science
Volume 2, Issue 11, November 2024
https://westerneuropeanstudies.com/index.php/3
ISSN (E): 2942-1918 Open Access| Peer Reviewed

therapy or surgical intervention has become a thing of the past. However, as it turns out, the results achieved through the introduction of bisphosphonates can be improved. The use of denosumab can significantly reduce the risk of developing RCM or delay the timing of their occurrence. Aversion to the development of pain syndrome and the patient's ability to lead a full life for a longer period of time. In addition to these clinical benefits, treatment with denosumab reduces the risk of renal toxicity and acute phase reactions, and allows for a more convenient route of administration via subcutaneous injection. Denosumab (Exgiva) is an effective, well-tolerated drug that increases the chance of preventing RCM in breast cancer. Thus, in patients with metastatic breast cancer, denosumab with long-term use gave better results in terms of time to the development of the first adverse outcome of skeletal lesions than zoledronic acid.

LITERATURE

1. Bagrova S. G. Asymptomatic bone metastases in breast cancer. "Treatment cannot be observed" - where can I put a comma? Malignant Tumors 2022; #3s1 : 39–42.
2. Bagrova S.G., Basin E.M., Valiev A.K., Dengina N.V., Kopp M.V., Kutukova S.I. et al . Prevention and treatment of bone tissue pathology in malignant neoplasms. Malignant tumors: Practical recommendations RUSSCO #3s2, 2021 (volume 11). 38.
3. von Moos R. Costa L. Gonzalez-Suarez E. et al. Management of bone health in solid tumors : from bisphosphonates to a monoclonal antibody. Cancer Treat Rev. 2019; 76: 57–67.
4. Coleman R, et al. Bone health in cancer: ESMO Clinical Practice Guidelines. Ann Oncol 2020: S0923–7534(20)39995–6.
5. NCCN Guidelines Version 1.2022. Adult Cancer Pain/ https:// www.nccn.org/guidelines/guidelines-detail?category=3&id=1413.
6. O'Carrigan B, Wong MH, Willson ML, et al: Bisphosphonates and other bone agents for breast cancer. Cochrane Database Syst Rev 10: CD003474, 2017.
7. Roger von Moosa , Jean-Jacques Bodyb , Alex Rid erc et al. Bone-targeted agent treatment patterns and the impact of bone metastases on patients with advanced breast cancer in real-world practice in six European countries. Journal of Bone Oncology 11 (2018) 1–9.
8. Guy Hechmati , A. Brett Hauber et al. Patients' preferences for bone metastases treatments in France, Germany and the United Kingdom. Supportive Care in Cancer 2323, pages 21–28 (2015).
9. Wang X, Yang KH, Wanyan P, Tian JH: Comparison of the efficacy and safety of denosumab versus bisphosphonates in breast cancer and bone metastases treatment: A meta-analysis of randomized controlled trials. Oncol Lett 7: 2014.
10. Atakhanova N.E, Almuradova D.M, Ismoilova U.A, Ziyaev Sh.V. Clinical and morphological Characteristics of breast cancer with triple negative phenotype. Web of medicine: Journal of Medicine, practice and nursing. Volume 1, Issue 8, November, 2023. www.Webofjournals.com/index.php/5 .
11. N.E Atakhanova ., D.M Almuradova ., N.I Tursunova ., Sh.V Ziyaev. Triple negative breast cancer and drug-resistant cells. World bulletin of public health (WBPH) in Volume 28. November, 2023. ISSN: 2749-3644
12. Atakhanova NE Almuradova DM Ziyayev Sh.V. Mathematical model for predicting survival in patients with triple negative breast cancer. ResearchJet Journal of analysis

Western European Journal of Medicine and Medical Science
Volume 2, Issue 11, November 2024
https://westerneuropeanstudies.com/index.php/3
ISSN (E): 2942-1918 Open Access| Peer Reviewed

and intervention Vol 4. Issue 11. November, 2023. Available at: https://researchjet.academiascience.org .
13. Алмурадова Д.М., Мирахмедова С.С. Оценка эффективности лечения трижды негативного рака молочной железы. Журнал Интернаука (2018). Т-44/1, 29-30.
14. Tilyashayhov M.N, Atakhanova N.E., Gaziyev L.T, Almuradov A, Алмурадова Д.М. Modern approach to diagnostics, prediction and course of renal cell cancer (2021). Annals of the Rumanian Society for cell biology T 1 (2), 4429-4451.
15. Tursunova N.I., Almuradova D.M., Mamajonov X.I., Ismailova U.A. Multiple Primary Cancer: Genetic Pathomorphological Factors of Endometrial and Breast Cancer. Texas Journal of Medical Science ISSN NO: 2770-2936. Date of Publication:08-09-2023.