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EFFICIENCY OF THE VINORELBINE – CAPECITABINE + BEVASIZUMAB REGIMEN IN THE TREATMENT OF PATIENTS WITH METASTATIC TRIPLE NEGATIVE BREAST CANCER

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Abstract

The most aggressive and unpredictable among the subtypes of breast cancer is triple negative breast cancer, which has high proliferative activity and a high growth rate, early leading to damage to internal organs and the central nervous system. In the presence of distant metastases, the median overall survival does not exceed 14 months. TNBC is an extremely heterogeneous group of tumors; it includes both tumors that are highly sensitive to chemotherapy and those that require targeted or immunotherapy to achieve the best treatment results. The heterogeneity of the group of triple negative breast cancer and the absence of conventional molecular targets for drug action (hormone receptors and HER-2/ neu amplification) explain the difficulties in choosing treatment tactics. Such subtype features make it difficult to develop a uniform treatment strategy for all patients. Current understanding of resistance mechanisms and molecular drivers of progression has expanded therapeutic options for metastatic TNBC (mTNBC). All this indicates the need to develop new antitumor therapy regimens that are not typical for other forms of breast cancer, which will improve the results of treatment for such patients.

Keywords: triple negative breast cancer, chemotherapy, metastasis, target therapy.

Introduction

Triple-negative breast cancer (TNBC) is characterized by a lack of expression of estrogen receptors, progesterone receptors, and HER2. Currently, this subtype is characterized by the most aggressive course and the lowest median overall survival (OS) among all breast cancer subtypes

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[1]. TNBC is a diagnosis of exclusion and therefore does not represent a single subtype, but rather a group of multiple tumor types united by the lack of hormone receptor and HER2 expression. Due to this heterogeneity, repeated attempts have been made to classify TNBC in order to further select the optimal treatment strategy [2–4]. The classification of TNBC was first presented by B. Lehmann et al . in 2011 [2]. The authors proposed a division into six molecular subtypes based on genetic analysis of 587 breast tumors. Two subtypes were classified as basal-like (BL1 and BL2). When comparing the achievement of complete pathological regression in 130 patients with TNBC who received neoadjuvant chemotherapy (CT), it was shown that those whose tumors corresponded to basal-like subtypes had a rate of 52%, while patients with mesenchymal tumors had a rate of 31%, and patients with androgen expression – 10% (p=0.043) [5]. The BL2 subtype was characterized by activation of genes responsible for pCR signaling pathways of growth factors (EGF, NGF, MET, Wnt /b- catenin), as well as activation of glycolysis and gluconeogenesis . The immunomodulatory (IM) subtype is characterized by a large number of immune cells infiltrating the tumor, as well as activation of signaling pathways in immune cells (TH1/TH2, NK, BCR, DC) and signaling pathways associated with cytokines. In addition, in such tumors the processes of antigen processing and presentation, as well as the main signal transduction pathways (NFKB, TNF, JAK/STAT), are activated. Mesenchymal (M) and mesenchymal subtype with stem cell characteristics (MSL) are characterized by activation of signaling pathways associated with tumor cell migration. In addition, the MSL subtype is often characterized by the presence of signaling pathways associated with growth factors: EGFR, PDGF, ERK1/2, but at the same time a low level of proliferation genes. Low expression of claudins 3, 4 and 7 is also characteristic of the MSL subtype. The latter, LAR subtype, is characterized by high expression of androgen receptors. Despite the seemingly obvious target of therapy, studies using antiandrogens (eg, bicalutamide) in AR-positive TNBC have not demonstrated the effectiveness of this approach [6]. Later, several more classifications were presented [3, 4], identifying similar subtypes. Currently, TNBC is widely divided into 4 subtypes: luminal-like , mesenchymal , basal-like with immunosuppression and basal-like immunoactivated [4]. These classifications are not widely used due to the high cost of conducting research. Nevertheless, they allow us to expand our understanding of possible points of application of therapy (for example, immunotherapy for basal-like immunoactivated subtype).

Despite the abundance of molecular signatures that can potentially be used to select optimal therapy, chemotherapy currently remains the mainstay of treatment for patients with metastatic TNBC (mTNBC) [7–9]. The main drugs for the treatment of mTNBC remain taxanes , platinum drugs and anthracyclines . CT in the 1st line allows achieving an objective response rate (ORR) in the region of 20–30% [10]. However, OS when using standard treatment methods does not exceed 12–14 months [11, 12]. The use of monotherapy or a combination of drugs remains controversial. In most cases, clinical recommendations agree on the use of monotherapy [7–9]. In cases where it is necessary to achieve a rapid response to therapy, the general functional status, as well as the patient's concomitant diseases, allow a more toxic treatment to be prescribed, combination therapy can be used [13]. There are several main mechanisms of resistance to chemotherapy in mTNBC. The study of resistance mechanisms underlies the development of new drugs that can improve patient treatment outcomes. First of all, with rapid tumor growth, chronic hypoxia can develop [14]. Low oxygen levels stabilize hypoxia-inducible factor (HIF), which allows cells to survive in

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difficult conditions. Hypoxia promotes the development of chemoresistance in several ways. First, poorly developed vasculature impedes drug penetration [14]. Secondly, the lack of oxygen and an acidic environment reduce the effectiveness of some drugs [15]. Third, hypoxia induces a tumor stem cell phenotype [16]. Fourth, hypoxia activates immunosuppressive signaling pathways and acts as a barrier to immune effector cells. Another mechanism is associated with ABC transport proteins (ATP- binding cassette), which use adenosine triphosphate to transport various compounds across the cell membrane, both into and out of the cell. Cells with increased activity of ABC transporters can become resistant to chemotherapy, transferring molecules outside the tumor cells, thus preventing their therapeutic potential from being realized. One of the key signs of tumor progression is dysregulation of signaling pathways: activation of cells responsible for proliferation and growth and suppression of cells inhibiting tumor growth [19]. All of these pathways are interconnected, and these connections are not fully understood. The problem with using inhibitors of these pathways is their toxicity and effect on normal human stem cells.

Immunotherapy is now an effective option for a large number of solid tumors. Clinical studies have demonstrated the feasibility of immunotherapy for TNBC. Several key characteristics make TNBC more likely to respond to immunotherapy than other breast cancer subtypes. First, TNBC has a higher number of TILs [17], which now has a proven predictive and prognostic role. Second, TNBC has higher levels of PD-L1 expression on both tumor and immune cells, providing direct targets for immunotherapy [18]. TNBC also has a higher number of nonsynonymous mutations that give rise to tumor-specific neoantigens that activate neoantigen -specific T cells to generate an antitumor immune response, which can be enhanced by checkpoint inhibitors.

A large number of clinical trials are currently underway to develop new drugs for mTNBC , and inclusion of patients in clinical trials is the preferred option.

Many issues of immunotherapy continue to be studied, and methods are being developed to modify the tumor immune environment in order to improve the prognosis of treatment of tumors that do not contain TILs. Unfortunately, most patients experience progression of the process during drug treatment. Current directions in the development of immunotherapy include the search for prognostic and predictive markers of the effectiveness of drug treatment, which will help individualize approaches to immunotherapy.

Purpose of the study. Evaluation of the immediate effectiveness of polychemotherapy + immunotherapy Vinerelbine + Capecitabine + Bevasizumab in the treatment of patients suffering from triple negative metastatic breast cancer (mTNBC).

Materials and methods of research. The study included 21 patients with metastatic TNBC . The age of the patients ranged from 35 to 66 years. The diagnosis of cancer was confirmed by histological and immunohistochemical methods. After signs of disease progression, patients underwent a comprehensive examination, including: clinical research methods; laboratory examination methods (general blood count, biochemical blood test, blood test for tumor marker CA 15-3, urinalysis, histological and immunohistochemical examination of the primary tumor and regional metastases); methods of visualization of metastases (ultrasound, osteoscintigraphy , CT, MRI, radiography).

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When assessing the timing of progression, it was noted that they ranged from 2 to 181 months, the median was 21.8 months. In a quarter of the patients, generalization of the process was detected within a period of 9.8 months. (first year of observation), four more

According to the results of the examination of patients, it was found that damage to one organ was observed in 13 (61.9%) patients, of which metastatic damage to the lungs was detected in 4 (30.8%) patients, distant lymph nodes - in 4 (30.8%) patients, bones - in 2 (15.4%) patients, damage to the liver only was observed in 7.7% of cases. 8 (38%) of 21 patients had multiple lesions of various organs and tissues. In particular, metastases to the lungs and liver occurred in 1 (12.5%) patient, metastases to the lungs and bones were diagnosed in 1 (12.5%) patient, metastatic lesions of the lungs and skin/soft tissues - in 1 (12.5%) %) patient, metastases to the lungs and distant lymph nodes - in 1 (12.5%) patient, metastases to the liver, skin and soft tissues - in 1 (12.5%) patient, metastases to the liver and distant lymph nodes were detected in 1 (12.5%) female patients. Multiple metastases to the skin, soft tissues and distant lymph nodes were diagnosed in 1 (12.5%) patient, metastases to the lungs, liver, lymph nodes - also in 1 (12.5%) patient. In our research 6 courses were carried out according to the following regimen: vinorelbine – 25mg/m2 intravenously on days 1 and 8, capecitabine – 2000 mg/m2 orally in the morning and evening from days 1 to 14 and Bevasizumab 7.5 mg/kg on the 1st day with an interval between courses of 21–28 days. 21 days after completion of the 3rd and 6th courses of PCT, ultrasound of the mammary glands, regional areas, MSCT of the chest and abdominal cavity with contrast was performed, determining the volume of the breast tumor and the size of the lymph nodes, metastatic tumor in the lungs and liver. 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 -2 test were used.

Research results

The number of courses ranged from 4 to 8. In 66.7%, 6–8 courses of chemotherapy were carried out, in 33.33% of cases - 4 courses. The assessment of the immediate therapeutic effect was carried out after 3, 6 and subsequent courses of chemotherapy. Disease control, complete and partial regression and stabilization of the tumor process were recorded in 14 (66.7%) patients. Complete regression of metastases was observed in 6/21 (28.6%) patients. The duration of remission varied with full effect from 4 to 12 months (average 8 months); with partial effect – from 1 to 7 months

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(average 4 months). The median time to progression with a complete effect was 7 months, and with a partial effect – 3.4 months.

In addition to assessing the overall immediate effect of chemotherapy, an analysis of the sensitivity of metastases was performed depending on their location. Metastatic lesions of the lungs were diagnosed in 9 (42.8%) patients, of which 4 (44.4%) patients had metastases to the lungs without involving other organs, and 5 (55.5%) patients had metastatic lesions of the lungs in combination with damage to other organs and tissues. The direct effect of chemotherapy on lung metastases was assessed. Thus, metastases to the lungs, both with and without concomitant lesions of other organs, turned out to be sensitive in 44.4% of cases when using the "bevacizumab + vinerelbine + capecitabine " regimen. Metastases to the liver were detected in 5 (23.8%) patients, of which in 4 (80%) patients - in combination with metastatic lesions of other organs, in 1 (20%) patient - without involvement of other organs and tissues (Table 3). Thus, liver metastases, both with and without concomitant lesions of other organs, turned out to be insensitive to the " bevacizumab + vinerelbine + capecitabine " regimen. 3/21 (14.3%) patients had bone metastases, of which 2 (66.7%) patients were diagnosed with metastatic bone lesions without involvement of other organs, and 1 (33.3%) patient was diagnosed with combined bone lesions and lungs. In cases of bone metastases, their partial regression was noted according to examination data (osteoscintigraphy , MRI) in 2 patients. The small number of patients with metastases to the liver and bones does not allow us to speak about the effectiveness of this chemotherapy regimen. However, it indicates that in some cases it is possible to achieve partial regression. Metastatic lesions of the skin and soft tissues were detected in 5 (23.8%) patients, of which 3 (60%) patients. Thus, metastases to the skin and soft tissues, both with and without concomitant lesions of other organs, turned out to be highly sensitive to chemotherapy according to the regimen of vinerelbine + capecitabine + bevasizumab, which allows achieving an immediate effect in 100% of cases. Metastases to distant lymph nodes were present in 8 (38.1%) patients, of which 4 (50%) patients had it in combination with damage to other organs and tissues, and 4 (50%) patients had lymph node damage without involvement of other organs. The immediate effect on metastases to the lymph nodes is presented in table. 6. It should be noted that metastases to lymph nodes are highly sensitive to chemotherapy with vinerelbine + capecitabine + bevasizumab . Of the toxic reactions when using the vinerelbine + capecitabine + bevasizumab regimen , grade 1–3 neurotoxicity was noted . in 16/21 (76.2%) patients, neutropenia grade 3–4. in 2/21 (9.5%) patients, thrombocytopenia 1st degree. in 1/21 (4.8%) patients, anemia of 1–2 degrees. in 5/21 (23.8%) patients. Complications during chemotherapy required a reduction in drug doses, phlebothrombosis of the deep veins of the lower extremities in 1 patient, and therefore chemotherapy was discontinued.

Conclusions

Triple negative breast cancer is an aggressive tumor subtype with a high risk of disease progression, early damage to internal organs and the central nervous system. Given the significant molecular heterogeneity, an interesting direction in the development of drug therapy for TNBC metastases is the study of regimens atypical for the treatment of breast cancer. Considering the small number of patients in the study group, it is not possible to make a final statement about the

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effectiveness of the developed regimen. This study demonstrates a general trend towards improved treatment outcomes for mTNBC with the use of new antitumor therapy regimens that are not typical for other breast cancer subtypes. Of course, further accumulation of material is required in order to formulate a final conclusion about the sensitivity or resistance of patients with mTNBC to an antitumor therapy regimen using bevasizumab . The study showed the effectiveness of a combination of antiangiogenic therapy+chemotherapy vinerelbine + capecitabine + bevasizumab is well tolerated and highly effective in patients with triple negative metastatic breast cancer.

References

1. Ganshina I.P., Gordeeva O.O., Manukyan M.Sh. Current treatment options for metastatic triple-negative breast cancer. Modern oncology. 2020; 22 (4): 60–65. DOI : 10.26442/18151434.2020.4.200495.

2. Lehmann BD, Bauer JA, Chen X et al. Identification of human triple-negative breast cancer subtypes and preclinical models for selection of targeted therapies. J Clin Invest 2019; 121(7):2750–67.

3. Jézéquel P, Loussouarn D, Guérin-Charbonnel C et al. Gene-expression molecular subtyping of triple-negative breast cancer tumors: importance of immune response. Breast Cancer Res 2022; 17:43.

4. Burstein MD, Tsimelzon A, Poage GM et al. Comprehensive Genomic Analysis Identifies Novel Subtypes and Targets of Triple-negative Breast Cancer. Clin Cancer Res 2020; 21 (7): 1688–98.

5. Masuda H, Baggerly KA. Wang Y et al. Differential response to neoadjuvant chemotherapy among 7 triple-negative breast cancer molecular subtypes. Clin Cancer Res 2013; 19:5533–40.

6. Gucalp A, Tolaney S, Isakoff SJ et al. Phase II trial of bicalutamide in patients with androgen receptor-positive, estrogen receptor-negative metastatic breast cancer. Clin Cancer Res 2023; 19:5505–12.

7. Gradishar WJ, Anderson BO, Abraham J et al. Breast Cancer, Version 3.2020, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw 2020; 18 (4): 452–78. DOI: 10.6004/jnccn.2021.0016; PMID: 32259783.

8. Cardoso F, Paluch-Shimon S, Senkus E et al. 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5). Ann Oncol 2023; 31 (12): 1623–49. DOI: 10.1016/j.annonc.2020.09.010

9. Stenina M.B., Zhukova L.G., Koroleva I.A. and others. Practical recommendations for drug treatment of invasive breast cancer. Malignant tumors. Practical recommendations RUSSCO #3s2 2019; 9: 128–63.

10. Olga V. Smirnova. Results of drug treatment of patients with metastases of triple negative breast cancer. Journal of Malignant Tumors Volume/ Vol . 7 No. 4 /2017. DOI:10.18027/2224–5057–2017–7–4–42–47

André F, Zielinski CC. Optimal strategies for the treatment of metastatic triple-negative breast cancer with currently approved agents. Ann Oncol 2012; 23(Suppl. 6): vi46–51.

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Licensed under a Creative Commons Attribution 4.0 International License.

11. Kassam F, Enright K, Dent R et al. Survival outcomes for patients with metastatic triple-negative breast cancer: Implications for clinical practice and trial design. Clin Breast Cancer 2022; 9:29–33.
12. Dent R, Trudeau M, Pritchard KI et al. Triple-negative breast cancer: Clinical features and patterns of recurrence. Clin Cancer Res 2007; 13:4429–34.
13. Zeichner SB, Terawaki H, Gogineni K. A Review of Systemic Treatment in Metastatic Triple-Negative Breast Cancer. Breast Cancer: Basic and Clinical Research, 2021.
14. 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 .
15. 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
16. Atakhanova NE Almuradova DM Ziyayev Sh.V. Mathematical model for predicting survival in patients with triple negative breast cancer. ResearchJet Journal of analysis and intervention Vol 4. Issue 11. November, 2023. Available at: https://researchjet.academiascience.org .
17. 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.
18. Алмурадова Д.М., Мирахмедова С.С. Оценка эффективности лечения трижды негативного рака молочной железы. Журнал Интернаука (2018). Т-44/1, 29-30.
19. Г.А Хакимов, Г.Г Хакимова, Н.Э Атаханова, Д.М Алмурадова, М.М Отабоева Современные взгляды на рак молочной железы у больных молодого возраста. ILM FAN XABARNOMASI. 1 (2) 101-110.

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