ISSN NO: 2770-2936
June 2024

APPROACHES TO THE TREATMENT OF METASTATIC BREAST CANCER

Umida Ismailova Abdullayevna[1],
Assistant of Oncology Department,
Tashkent Medical Academy.
Atahanova Nigora Ergashevna[2]
Professor of Oncology Department,
Kurbankulov Uktam Muhammadovich[3]
Associate Professor of Oncology Department,
Tashkent Medical Academy, PhD.
Jumanazarov Azizbek Ulugbekovich[4]
Assistant of Faculty and Hospital Surgery Department №1,
Tashkent Medical Academy

Annotations
Progress in the treatment of this disease, metastatic dissemination is still considered an inclusive condition. In this lecture will be considered questions of «non-standard» therapy, which may be included in our practice in the future.
Keywords:Metastatic Breast Cancer, High-Dose Chemotherapy, Metronome Therapy, Vaccine Therapy, Adoptive Therapy

Introduction: Drug treatment of patients with metastatic breast cancer (mBC) represents one of the most difficult problems of clinical oncology. First of all, this is due to the heterogeneity of the disease (biological, kinetic, etc.); moderate sensitivity of the tumor to chemo- and hormone therapy and the absence of absolute signs of resistance to modern antitumor drugs, the prescription of most of which is empirical and based on the statistical probability of a positive effect. When assessing the probability of a positive effect of antitumor treatment, clinicians, as a rule, can rely only on certain phenotypic characteristics: histological type of tumor, degree of its differentiation, general condition of the patient, etc. Improvements in drug therapy lead to an improvement in the quality of life of patients, but are not accompanied by an increase in overall life expectancy and a decrease in mortality. It is assumed that identification of tumor-specific mutations and gene expression changes, study of drug resistance or sensitivity mechanisms (intratumor drug metabolism (activation/inactivation), availability of targets and their accessibility) will significantly improve the results of antitumor therapy. In the treatment of mRCC patients, the following objectives are set: prolongation of life and symptom control (increasing the relapse-free period and reducing the toxicity of treatment). The effectiveness of therapy can be improved through the synthesis of new antitumor drugs, the use of new regimens of "old" drugs (very low or high doses of cytostatics, prolonged infusions, weekly injections), individualization of therapy and immunotherapy (antibodies and check-point inhibitors). Such types of "non-standard" therapies as vaccine therapy, cytokines, virotherapy, and adoptive cell therapy are being actively studied.

High-dose chemotherapy

Great hopes are pinned on the use of cytostatics in myeloablative doses - high-dose chemotherapy (HDCT) with transplantation of autologous hematopoietic stem cells. This is based on numerous clinical and experimental studies that have shown a direct correlation between the dose of cytostatics and antitumor effect [1]. A number of randomized trials have been conducted in which high doses of cytostatics used for therapeutic purposes in patients with disseminated breast cancer were studied [2]. The main objective of the conditioning regimen is to kill tumor cells. Increasing the doses of cytostatics in polychemotherapy regimens by 100% or more in mRMM patients resistant to standard chemotherapy is accompanied by a clinically significant increase in the rate of objective responses. Unfortunately, relapse of the underlying disease remains the main cause of high-dose treatment failure [3]. High-dose carboplatin, thiophosphamide, and cyclophosphamide are used in

ISSN NO: 2770-2936
June 2024

one of the most common regimens for the treatment of cancer patients. Other high-dose regimens include cyclophosphamide, etoposide, cisplatin and adriamycin (CEP) or busulfan, melphalan and thiophosphamide (Bu/Mel/T) [4]. It should be borne in mind that such treatment in all patients is accompanied by a high risk of developing certain complications of III-IV degree of toxicity, which threaten lethal outcome. In the future, patients have inevitable progression of the disease, requiring active treatment measures. Bone marrow reserves after VDCT are very limited - with this in mind, the choice of cytostatics is narrowed due to the risk of severe toxic reactions and requires the appointment of reduced doses. Because of this, as well as the potentially high risk of life-threatening complications, VDCT in mRMM is of very limited value [5]. V.F. Borges et al. analyzed 6 randomized trials on mRMM. They involved 844 patients. They achieved statistically significant improvement in progression-free survival (median 11 and 8.3 months; HR, 0.76; p The use of nonmyeloablative chemotherapy regimens with hematopoietic stem cell transplantation for the treatment of disseminated solid tumors is the logical conclusion of almost fifty years of experimental and clinical studies of the role of immune mechanisms in the treatment of malignant neoplasms by allogeneic bone marrow transplantation. Few researchers have performed allogeneic hematopoietic stem cell transplantation for non-hematologic malignancies because of the high mortality of patients. Two transplantation groups have used allogeneic bone marrow transplantation in RRM. In 1996, Eibl et al. first described a graft-versus-tumor (GTV) effect in a woman with mRML after high-dose radio-chemotherapy with allogeneic bone marrow transplantation from an HLA-identical related donor. The authors observed a decrease in liver metastases against the background of the developed graft versus host reaction (GTR). It was found that lymphocytes in the post-transplantation period showed specific cytotoxic activity against cells of the RCC lineage, which confirmed the presence of a tumor-specific allogeneic response in this patient. In 1998, N.T. Ueno et al. (staff of the American M.D. Anderson Cancer Center) also used high-dose radio-chemotherapy with allogeneic bone marrow transplantation in the treatment of patients with mRML. Some patients achieved a response, presumably due to a TPO effect, but transplant-related mortality was still high in this group of patients [7]. Patient selection is the key to optimizing treatment outcomes. The best results were observed in patients who received VDCT at earlier stages of the disease, when the tumor size and the number of resistant clones are small. Recently, there has been promising information about treating patients with BRCA mutations and giving them high-dose platinum-based chemotherapy. BCM patients with BRCA mutation are highly sensitive to DNA-damaging agents. L. Boudin et al. (Institut Paoli-Calmette, Marseille, France) retrospectively analyzed 235 patients from 2003 to 2012 who received VDCT with cisplatin and autologous hematopoietic stem cell transplantation. In multivariate analysis, BRCA status (mut) was an independent prognostic factor for OVOS (hazard ratio (HR): 3.08, 95% confidence interval (CI): 1.10-8.64, P=0.0326) and VBPPFS (HR: 2.52, 95% CI: 1.29-4.91, P=0.0069) [8]. In mRCC treatment guidelines, the administration of intensified chemotherapy regimens (with prophylactic administration of colony-stimulating factors) is considered for high proliferative activity RCC. VDCT with hematopoietic stem cell support is not recommended.

Metronomic therapy

In contrast to VDCT, low-dose cytostatic therapy - metronomic therapy - is actively entering our practice. In this case, "standard" cytostatics are administered in doses much lower than necessary to obtain a "direct" antitumor effect, but sufficient to damage the endothelium of tumor vessels. Such doses are practically not accompanied by side effects, which makes it possible to use cytostatics continuously for a long time without giving an opportunity for repair of damaged endothelial cells [9]. The use of endothelial cells as a "target" can potentially avoid or significantly delay the emergence of resistance, because unlike tumor cells, the endothelial cell genome is stable and not subject to mutations. Preliminary studies on metronomic chemotherapy in a number of neoplasms have very encouraging results. Metronomic therapy has a direct effect by suppressing circulating endothelial stem cells and having an antiproliferative effect on endothelial cells, and indirectly by increasing the level of endogenous thrombospondin 1, which leads to apoptosis of CD36 positive endothelial cells; reducing mobilization of endothelial stem cells; blocking VEGF; inhibiting matrix metalloproteinases and tissue plasminogen activator [10]. One of the most common metronomic therapy regimens is cyclophosphamide 50 mg/day. per os daily long term and methotrexate 2.5 mg x 2 times daily days 1 and 2, weekly. The use of such a regimen in 63 mRMM patients, the overwhelming majority of whom had previously received chemotherapy for metastatic disease, allowed to achieve an objective response (PD + PR) in 19% of patients, and the overall efficacy of the regimen (including stabilization of the disease for six months or more)

ISSN NO: 2770-2936
June 2024

was 32%; did not have disease progression for at least one year 26% of patients. The toxicity of therapy was minimal [11]. Regimens that combine metronomic therapy with targeted antiangiogenic agents may be successful. In a phase II study comparing the efficacy and tolerability of metronomic therapy with methotrexate and cyclophosphamide and its combination with bevacizumab (10 mg/kg intravenously every 2 weeks) in the second-line treatment of mRMM, enrollment of patients in the group without bevacizumab was discontinued. The overall efficacy in the combined treatment group (metronomic chemotherapy + bevacizumab) was significantly superior to the comparison group and amounted to 29%; disease stabilization was observed in 41% of patients. The average time to progression in patients in the metronomic therapy group was only 2 months, while in the combined treatment group it was 5.5 months. There were no statistically significant differences when assessing the quality of life of patients in both groups or significant side effects [12]. Most clinical studies on metronome therapy address the following aspects: 1. metronomic therapy as an alternative to "conventional" chemotherapy, but with a more favorable safety profile; 2. the use of metronomic therapy as a maintenance regimen after standard chemotherapy, in order to prolong the efficacy of cytotoxic treatment; 3. its use in combination therapy as an antiangiogenic or immunologic agent.

Immunotherapy

Breast cancer is not traditionally considered an immunogenic tumor, but interest in immunotherapy for this disease has increased markedly today [14]. Interestingly, the emergence of antibodies against breast cancer targets may precede the clinical manifestation of the disease [15]. In six prospective studies of neoadjuvant chemotherapy that included a total of 3771 patients, the presence of more than 10% TIL (tumor-infiltrating lymphocytes) was observed in 71%, 56%, and 45% of triple-negative RRMS (TNRMS), Her2-positive, and luminal/Her2-negative tumors, respectively [16]. Importantly, the so-called "lymphocytic predominance" phenotype (>60% TIL) was observed in 30% of TNRML, compared to 19% and 13% of Her2-positive and luminal/HER2-negative tumors, respectively. Most interestingly, a linear relationship between TIL and the probability of regression after neoadjuvant chemotherapy was observed in all tumor subtypes. However, in terms of survival outcomes, a positive effect was observed only for TNRMJ and Her2-positive tumors, whereas luminal/Her2-negative tumors showed worse OS if the tumor had high TIL levels. One of the major challenges in immunotherapy of RRM is its molecular heterogeneity, which may explain the different immunogenicity [17]. Based on the strategy to target immunity, studies are being conducted in patients with RRM, which include: new variants of adoptive cell therapy [18-20], vaccine therapy, [21-23] and Checkpoint inhibitors. The possibility of genetic redirection of T-lymphocytes via artificial tumor-specific receptors expands the boundaries of application of adoptive cell therapy. These can be generated ex vivo by combining lymphocytes with tumor-specific T-cell receptors (TCRs) or chimeric antigen receptors (CARs), which is more specific for breast cancer. The development of effective vaccines against breast cancer for both therapy and prevention depends in part on the identification of breast tumor antigens that function as targets on the tumor cell. Many endogenous proteins induce tumor-specific T cells that help recognize the neoplasm. T cell function can be hampered by intrapathogenic changes that mask tumor cells, by heterogeneous expression of tumor antigens in the primary breast tumor or in metastases, or by evasion of immunity by suppression of the tumor antigen itself in breast tumors. The effect requires a vaccine platform that includes multiple antigens required for cellular transformation and tumor recognition targets. New information on the genomic and proteomic classification of breast tumors should accelerate the identification of novel tumor antigens central to the initiation, progression, and metastasis of breast cancer. The Her-2 protein is a classic example, and the clinical success of trastuzumab and pertuzumab as Her-2-specific monoclonal antibodies establishes Her-2 as the first truly validated target for breast cancer immunotherapy. Targets to the Her-2 protein and MUC-1 have been the most widely used in research [24]. As an alternative to antigen-specific vaccination based on peptides or protein subunits, vaccine platforms derived from cell extracts or whole tumor cells are being developed.

Studies combining immunotherapy and a cytostatic agent

NCT02309177	Opdivo and Abraxane immunotherapy for recurrent Her2- mRMW
NCT03206203	Carboplatin and Atezolizumab for metastatic TNRML
NCT02648477	Keytruda and chemotherapy or aromatase inhibitor for HER2- mRMG

ISSN NO: 2770-2936
June 2024

NCT02752685	Keytruda and Abraxane in HER2-negative mRMG
KEYNOTE-355	Keytruda and chemotherapy in patients with metastatic TNRML
NCT03121352	Keytruda and two types of chemotherapy for metastatic TNRML
NCT03051659	Halaven and Keytruda for hormone-positive mRML
NCT02768701	Cyclophosphane and Keytruda for metastatic TNRML
NCT03044730	Keytruda and Xeloda for mRML
NCT02111850	T-cell immunotherapy for mRMMC (anti-MAGE-A3)
NCT02239861	Vaccine targets five common tumor-bearing antigens: NY-ESO-1, MAGEA4, PRAME, Survivin and SSX.
NCT02536794	MEDI4736 and tremelimumab in patients with Her2- mRMG.

These have the advantage that they themselves carry polyvalent immunization. Thus, cell-based vaccines have the advantage of delivering multiple antigens, increasing the likelihood of incorporating the most effective immune antigens and reducing the likelihood of tumor immune "escape" due to evolutionary variants of antigen-specific loss. Most clinical data evaluating the efficacy of an anti-RMV vaccine describe therapies targeting Her-2 or carbohydrate antigens such as MUC-1. Some phase I, II, and III studies of RRM vaccines are summarized in Table 3. Many vaccines induce detectable tumor-specific antibodies and/or anti-tumor CD8+ T-cell responses. However, inclusion of only one component of the immune system is not sufficient for an effective therapeutic response. Therefore, a vaccination strategy must include some combination of multiple immune mechanisms, including CD4+ and CD8+ T cells, antibody-secreting cells, and innate immune effectors. Suppressive mechanisms in the tumor microenvironment inhibit the activity of vaccine-induced immune responses. Thus, RRMS vaccines as the sole therapeutic agent are unlikely to be clinically effective, especially in advanced disease. A number of challenges exist when administering immunotherapy in mRMW patients. Immune tolerance increases with disease progression. Patients with stage IV disease require standard treatment, and this in turn can both promote and counteract the antitumor immune response. Therefore, an evidence-based approach to combining standard treatment and vaccine therapy is needed. Most of these studies concern combinations of immunotherapy and various types of chemotherapy and hormone therapy, and sometimes radiation therapy. Studies are emerging where a new cytotoxic or targeted agent is being studied in combination with immunotherapy. In the setting of a normally functioning immune system, the effect of some antitumor drugs may be greater. Immunotherapy will be most effective when there is minimal residual disease. For patients with advanced disease, breast cancer vaccines should be combined with standard therapy. Drugs that alter the immunologic milieu (cyclophosphamide and paclitaxel) or the biology of the RRM (endocrine therapy and trastuzumab) are required to enhance vaccine activity. Clinical trials that combine immunomodulatory drugs and vaccines against RMH require a comprehensive understanding of the immune tolerance and immunobiology of patients, as well as knowledge of the pharmacodynamic interactions between the immune response and different drugs [25]. Interesting preliminary results from the Sacituzumab Govitecan (IMMU-132) study have recently been reported. The drug is a monoclonal antibody against TOP-2, which occurs in 90% of TNRMJTNBC patients. Of the 60 patients included, the overall response was gender Supporting Methods Results are pending from a phase II study (NCT03072992) investigating treatment with curcumin (CUC-01, yellow solution), 300 mg and paclitaxel 80 mg/m2, i.p. once weekly for 12 weeks versus monotherapy with paclitaxel 80 mg/m2, and placebo solution 250 mL, once weekly for 12 weeks. Results

ISSN NO: 2770-2936
June 2024

from the phase III BELLE-3 study were presented at the San Antonio Cancer Symposium. They suggest that the combination of the PI3K inhibitor buparlisib with hormone therapy is effective in treating patients with advanced hormone-dependent cancer who have disease progression after therapy with everolimus and exemestane. The median WBP was 3.9 months in the buparlisib group and 1.8 months in the placebo group. The 6-month UBP rates were 30.6% and 20.1%, respectively. Recalling the mechanism of action of aspirin, which also blocks the PI3K signaling pathway, new directions for clinical research are opening up here [27]. It is known that the use of antioxidants reduces toxic manifestations of chemotherapy (coenzyme Q10 - cardiotoxicity, alpha-lipoic acid, vitamin E - polyneuropathy), but they have no effect on life expectancy. Theoretically, they can reduce the effectiveness of HT, as a number of drugs work due to oxidative damage of tumor cells.in 30%, and the time without progression in patients with resistant CRC was 6 months. [26].

Conclusion

Breast cancer is a heterogeneous disease. For example, among TN breast cancers there are 6 subtypes, each of which can be treated differently. For basal-like cancer, platinum and taxanes will be highly effective, for immunomodulatory cancer - immunotherapy, for mesenchymal cancer - drugs affecting signaling pathways - PI3K, mTOR, Scr, and for luminal androgen-receptor type - androgen receptor antagonists (for example, Bicalutamide) will work. Thus, breast tumors are a conglomeration of numerous syndromes with characteristic molecular features, with different course and unequal sensitivity to treatment. To maximize the effect, the right treatment for the right indications should be given to the right patient at the right time.

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