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THE PLACE AND ROLE OF IMMUNOTHERAPY IN THE TREATMENT OF DISSEMINATED BREAST CANCER

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SUMMARY

The end result of the efficacy of cytostatic and targeted therapy for disseminated breast cancer for a long time deprived the oncological community and patients of hope for the possibility of drug cure for patients with metastatic tumors. The discovery of a new method for modulating the immune response and the related achievements in the field of tumor immunotherapy at a certain stage instilled optimism. This review provides an analysis of data on the role and place of immunotherapy in the treatment of disseminated breast cancer.

KEYWORDS: breast cancer, immunotherapy.

Inhibitors of immune checkpoints (IICPs) have shown their advantage over standard methods in many malignant neoplasms, both in efficiency and in tolerance, and have also demonstrated the possibility of a significant increase in the proportion of patients with long-term preservation of disease control. In 2019, Elvire Pons-Tostivint et al published the results of quantifying the proportion of patients who had sustained IICP responses compared with other drug classes. To assess the frequency of achieving long-term remissions and long-term survival, in the case of IICP and standard comparison therapy, the authors selected randomized phase III trials published between 2000 and 2018, in which at least one of the branches was represented by immunotherapeutic drugs (pembrolizumab, nivolumab, atezolizumab, ipilimumab, durvalumab, tremelimumab). In this paper, in order to formalize the term "long-term response" in terminological terms, the researchers arbitrarily defined remission that lasted three times longer than the median progression-free survival for all groups of patients receiving IICP. The main condition for assigning a patient to the category of patients with long overall survival was life expectancy at least twice the median overall survival for all patients included in the study in which the treatment was carried out. 19 studies were selected, which included a total of 11640 patients, divided into 42 study groups (26 groups received IICP, 16 - comparison therapy). Of the 16 comparison treatment groups, 11 used chemotherapy, one received targeted therapy, 3 groups received a placebo, and one used a vaccine. 12 out of 19 analyzed studies included previously pretreated patients (II and more lines of treatment). Crossover to the control group was acceptable in 5 studies (26%). With a median median follow-up of 15.7 months (range 5 to 38 months), the median median progression-free survival did not differ significantly between patients treated with IICP inhibitors and comparison therapy, being 3.8 months (95% CI, range 2.9 to 4.0 months), respectively. However, the average proportion of patients who achieved long-term remission, according to the definition adopted in the study, was 2.3 times higher among those who received IICP. The mean median overall survival also differed, which was 14.6 months in the IICP groups versus 11 months in the control group. Multivariate analyzes in this study demonstrated that the use of anti-PD-1 / PDL-1 therapy and the use of IICP as the first line of treatment were independent factors associated with the achievement of long-term remission. In 2020, the results of a systematic review and meta-analysis of the clinical efficacy and safety of anti-PD-1 / PDL-1 inhibitors in the treatment of advanced breast cancer were published. The authors of this work have demonstrated a greater efficacy of the above group of drugs in comparison with traditional methods of treatment and presented reliable evidence of a balance between the safety and benefits of IICP. In addition, the researchers pointed out a special benefit of anti-PD-1 / PDL-1 inhibitors in patients under 65 years of age, in smokers, without metastatic lesions of the central nervous system or liver, without a mutation in the epidermal growth factor receptor (EGFR) gene, and in the presence of high expression PDL-1. According to the authors, the study had a number of limitations:

1. The data obtained were based solely on the actual results of the study, and not on the results of individual patients.
2. Failure to exclude the influence of variables other than treatment that may have influenced the effectiveness of

anti-PD-1 / PDL-1 inhibitors due to differences between studies.
3. The prevalence of research on the effectiveness of immunotherapy inhibitors.
4. The prevalence of studies on the effectiveness of the inhibitor of anti-PD-1.
5. Most of those included had an open design, as a result of which, in the control group there could be patients who did not receive drugs in strict accordance with the planned distribution.
6. Due to the lack of baseline data, it was not possible to perform subgroup analyzes based on more anti-PD-1 / PDL-1 cut-off values, as well as to determine the portraits of patients who benefit most from treatment with these agents.

Despite certain successes of IICP in the first, second and subsequent lines of therapy for a wide variety of cancers, modern immunotherapy approaches are not the best treatment for all patients.

A universal tumor, a non-specific mechanism of action of this group of drugs, independent of the classical predictive factors of the effectiveness of chemotherapy or targeted therapy, provided a pronounced spread in the frequency of objective responses, the rarity of ultra-long responses in most cases. This situation initiated the beginning of an active search for predictive factors that would provide treatment for patients with a high chance of achieving the effect of IICP. Unfortunately, to date, only a few criteria have been identified, with the help of which one can try to increase the expected effectiveness of drugs. The first and most common predictive markers were the expression of PD-L1, as well as derived methods for its calculation (TPS, CPS). The presence of PD-L1 expression actually made it possible to identify patients with a higher chance of responding. However, even with a cut-off level of 50% or more expressing cells, not all respond to treatment, as well as low expression rates, there are patients who benefit from anti-PD-L1 therapy and have pronounced and lasting responses. Criticism of PD-L1 expression is based on the fact that in the case of spontaneous or induced changes in intracellular signaling cascades, this marker will not reflect the existence of real anti-tumor immunity, which was blocked by induction of PD-L1 expression by tumor cells. In addition, the determination of the expression of this protein in a tumor is associated with a number of problems due to its variability over time, depending on treatment and the presence of expression on stromal cells.

A marker associated with a high number of mutations, microsatellite instability, the occurrence of which is determined by disturbances in the operation of the unpaired base correction system, has been successfully integrated into routine practice. However, the incidence of this disorder is low, and its absence does not mean that there is no chance of success from the use of IICP. The mechanism of action of IICP assumes that the antitumor effect can develop only under the condition of a naturally formed immune response, and the presence of activated T-lymphocytes in the tumor, capable of specifically recognizing antigens that distinguish malignant cells from normal ones. The understanding of the importance of studying antitumor immunological reactions, as well as the search for predictive markers of hyperprogression and validated tests aimed at detecting primary and secondary immunoresistance are beyond doubt. Obesity, which is a serious medical and social problem, has hardly been studied until a certain point in terms of its influence on the antitumor immune response. In 2019, Rivadeneira D.B. et al published the results of a study in which they identified adipokine leptin as a potent tumor microenvironment remodeling agent that enhances the metabolic function of T cells. However, another preclinical study described the paradoxical effect of obesity on immune responses, expressed in T-cell depletion in mice with different tumor models with the participation of leptin-mediated signaling, which in turn led to higher PD1 expression and increased sensitivity to IICP. New data from a large analysis combining the results of four studies (one phase 3 KLA study and 3 phase 2 studies POPLAR, BIRCH, FIR) on the efficacy and safety of atezolizumab revealed a direct relationship between an increase in body mass index (BMI) and overall survival in patients in the atezolizumab group. The purpose of the analysis was to assess the relationship between BMI and overall survival, progression-free survival, and the incidence of treatment-related adverse events. The authors found a direct relationship between an increase in BMI and overall survival in patients receiving atezolizumab. Obesity was associated with a significant improvement in life expectancy in patients treated with atezolizumab as opposed to those treated with docetaxel. The correlation between better survival and BMI was most pronounced in the subgroup of patients with high PD-L1 expression. The risk of death was reduced in patients with the PD-L1 expression category in the obese group by 64% and in the overweight group by 31%. The risk of disease progression was also lower in the obese and overweight groups. BMI did not affect the incidence of therapy-related adverse events. A high BMI appears to be independently associated with improved survival with atezolizumab therapy. In the future, baseline BMI should be considered when planning clinical trials and considered as a stratification factor. Obesity should not be seen as a positive prognostic factor, but rather as a mediator of immune dysfunction and tumor progression, which can be successfully influenced by inhibiting PD-1 / PD-L1. Based on the information described above, we can talk about the emergence of an additional predictive factor that can better identify the cohort of patients with the greatest potential benefit from IICP. It becomes clear that BMI should be considered when stratifying patients in randomized clinical trials, see Objective. Reducing the risk of systematic errors in the analysis of their results. Studying the mechanisms of the influence of obesity on the effectiveness of immunotherapy can serve as the

basis for the creation of new drugs that potentiate the effect of IICP. None of the markers alone can serve as an absolute predictor, since the development of the antitumor immune response at each stage is influenced by many factors and the solution to the problem lies only in the complex assessment of the variables. Deep personification based on knowledge of the mechanisms of formation of the antitumor immune response in each specific situation seems promising, but from the standpoint of practical application, it is not yet feasible. It is possible that the focus of further research will be switched to the central regulation of the immune system.

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