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Therapeutic methods in the treatment of triple-negative breast cancer - a review

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Abstract

Breast cancer is a common female malignancy characterized by the presence of multiple subtypes taking into account, among other things, hormonal activity. The purpose of this study is to show the therapeutic options for triple-negative breast cancer (TNBC). A review of the literature in databases such as PubMed, Google Scholar, and Web of Science by keywords was performed, taking into account papers from 2017-2022. The main therapeutic approaches are surgical intervention and systemic chemotherapy (neoadjuvant and adjuvant). Unsatisfactory results from chemotherapy have prompted researchers to work on other methods to combat TNBC. Clinical trials are being conducted on the use of immunotherapy focusing mainly on

molecules against PD-1, PD-L1, and CTLA-4. Targeted therapy is the latest proposed form of therapy, which offers the possibility of introducing a drug in the future that will be tailored to the patient's needs limiting the negative therapeutic impact.

Keywords: breast cancer, triple-negative, treatment, surgery, chemotherapy, immunotherapy, targeted therapy

INTRODUCTION

Breast cancer is one of the most commonly diagnosed oncological diseases in women all over the world. This cancer is characterized by a disturbance of the cell cycle, resulting in uncontrolled and abnormal cell proliferation. The above disorders may be affected by gene mutations, hormonal factors, as well as environmental factors (e.g. age, gender, race). There are several ways to classify breast cancer, one of which is the division based on the morphology of the neoplastic lesion. Taking into account the degree of infiltration of the basement membrane, there are non-invasive carcinomas (in situ carcinomas) and infiltrating carcinomas distinguished. The types of non-invasive breast cancer are ductal and lobular carcinomas, and infiltrating cancers include ductal, lobular, colloidal, tubular, inflammatory, and cancer with features of medullary carcinoma. In addition to the above classification, there is also a clinical division that includes four groups: luminal A, luminal B, basal, and human epidermal growth factor receptor 2-enriched (HER2-enriched) [1, 2].

Globally, breast cancer ranks second after lung cancer in terms of the incidence of both genders. Nevertheless, this neoplasm has a relatively favorable prognosis, therefore it ranks only fifth in the world ranking of deaths from oncological disease [3]. However, among women in Poland and the United States, breast cancer is the most common and second cause of cancer death [4, 5].

There are many options for treating breast cancer and choosing the right one depends on many factors. The clinical and pathomorphological evaluation of the neoplasm has a significant influence on the procedure. In the clinical aspect, factors such as the size, location of the primary tumor, assessment of the axillary lymph nodes, and the presence, location, and extent of metastases are important. Histological type, grade, estrogen receptor (ER) / progesterone receptor (PgR) expression, Ki67, and HER2 are pathomorphological determinants of treatment [4]. Therapeutic methods include local and systemic actions. The first group includes surgical intervention and radiotherapy, while systemic methods include chemotherapy, hormone therapy, immunotherapy, and molecularly targeted therapy [6, 7]. This review focuses on treatment options for the breast cancer subtype named triple-negative (ER, PgR, and HER2 negative).

THE AIM OF THIS REVIEW

The review aims to present the therapeutic management and treatment options for triple-negative breast cancer.

MATERIALS AND METHODS

The study uses the method of non-systematic review of scientific literature. Databases such as PubMed, Google Scholar, and Web of Science were reviewed according to the keywords: breast cancer, triple-negative, treatment, surgery, chemotherapy, immunotherapy and targeted therapy. The analysis included articles from 2017 to 2022 with no restrictions on the method of the research.

TRIPLE-NEGATIVE BREAST CANCER TREATMENT

It is estimated that about 10-15% of breast cancers are in the triple-negative subtype. This cancer is characterized by the lack of expression of estrogen and progesterone receptors, as well as HER2. The above-mentioned features are factors that make it difficult to select an effective treatment because hormone and anti-HER2 therapy are ineffective. The most common method used in the treatment of TNBC is neoadjuvant chemotherapy and surgical intervention. Potentially low treatment options and clinical features such as high invasiveness, the propensity to relapse, and high metastatic potential encourage scientists to intensively research the development of modern therapeutic methods. Currently, much attention is paid to immunotherapy and targeted therapy [8, 9, 10, 11].

Neoadjuvant therapy

Despite numerous studies on obtaining newer therapies for TNBC, chemotherapy remains the mainstay of treatment. This type of neoplasm is recommended to use neoadjuvant therapy before surgical intervention. Based on the response from neoadjuvant chemotherapy (NACT), surgical treatment can be de-escalated and prognostic factors can be determined, which is then used to determine adjuvant chemotherapy. Approximately 30-40% of TNBC patients treated with standard anthracycline- and taxane-based NACT has been observed a pathologic complete response (pCR) with no histological evidence of invasive disease. Compared with patients with residual invasive disease, NACT patients show a relative reduction in the relative risk of cancer recurrence of approximately 70%, indicating that this type of chemotherapy contributes to better long-term outcomes [12, 13, 14].

Immunotherapy

Due to the poor response and the short survival time of patients after systemic chemotherapy, there was a need to introduce another therapy that would bring better results. Immunotherapy has been applied using the features of TNBC, such as greater genetic instability and complex structural rearrangement, which may indirectly increase the immunogenicity of this tumor. This method uses monoclonal antibodies against PD-1 (e.g. pembrolizumab, avelumab), PD-L1 (e.g. atezolizumab) and CTLA-4 (e.g. ipilimumab). Immunotherapy using these antibodies generates sustained responses [15, 16, 17].

The conducted clinical trials have shown that PD-1 / PD-L1 inhibitors are characterized by high clinical activity against TNBC and their use may bring therapeutic benefits. The Phase Ib JAVELIN trial, which included the monotherapy of the PD-1 inhibitor avelumab, showed that in 58 patients with TNBC, the Disease Control Rate (DCR) was 31% (18/58), while the Overall Response Rate (ORR) was estimated at 5.2% (95% CI, 1.1% -14.4%). Differences in ORR were also observed in terms of the presence of PD-L1 expression. Patients who were PD-L1 positive achieved higher ORR scores than PD-L1 negative patients, 22.2% (2/9) and 2.6% (1/39), respectively. However, the above study confirms that avelumab monotherapy's insufficient therapeutic efficacy [15, 16].

Pembrolizumab is another monoclonal antibody that has been studied in clinical trials for the treatment of TNBC. One of them was the KEYNOTE-355 trial, which included patients from 29 countries, taking into account PD-L1 expression. After selection, the study included 847 women with de novo metastatic TNBC and those who completed stage I-III breast cancer treatment who meet the following criteria: at least a 6-month interval between the end of treatment (adjuvant radiotherapy does not require a 6-month interval) and documented local or distant recurrence [18].

Progression-free survival of patients with a Combined Positive Score (CPS) PD-L1 equal to or greater than 10 was significantly different between the chemotherapy and pembrolizumab groups and those receiving a placebo instead of antibody treatment. In the first group, the progression-free survival at 6 months was 65.0% and at 12 months it was 39.1% (the median was 9.7 months, HR for progression or death, 0·65, 95% CI 0·49–0·86; one-sided p=0·0012). Over the same period of time, the rates for patients receiving placebo were 46.9% and 23.0%, respectively (median 5.6 months, HR for progression or death, 0·65, 95% CI 0·49–0·86; one-sided p=0·0012), which is significantly less than for patients receiving pembrolizumab [18, 19]. A similar relationship was observed in the group of patients with CPS PD-L1 equal to or greater than 1, where among those receiving pembrolizumab, the progression-free survival rate was 56.4% and 46.6% sequentially at 6 and 12 months (median 7.6 months , HR 0.74, 95% CI 0.61–0.90; one-sided p = 0.014), while in the latter group 31.7% and 19.4%, respectively (median 5.6 months, HR 0.74, 95 % CI 0.61–0.90; one-sided p = 0.014). Increased PD-L1 expression increases the effectiveness of pembrolizumab use, which is confirmed by the median progression-free survival rate in patients with CPS PD-L1 below 1. Among those who received the pembrolizumab-chemotherapy scheme, the median was 6.3 months, and 6.2 months for the placebo-chemotherapy scheme. The difference between these results is small, which in comparison with the previous groups of patients dependent on CPS PD-L1, may indicate the dependence of the effectiveness of pembrolizumab therapy in combination with chemotherapy on PD-L1 enhancement [18].

Targeted therapy

There are a number of pathways, receptors, and molecules that have recently attracted a lot of interest from researchers because they could be therapeutic targets for TNBC. PI3K/Akt, Notch, Hedgehog signaling pathways, epidermal growth factor receptor (EGFR), vascular endothelial growth factor (VEGF) and poly(ADP-ribose) polymerase (PARP) may be potential targets [20, 21]. In addition, microRNA molecules (miRNAs) or long non-coding RNAs (lncRNAs) may have an important function, not only in the treatment but also in the diagnosis and prognosis of TNBC [22, 23]. Tumor sequencing, which influences the identification of targets and thus the selection of drugs targeting those specific sites, as well as the knowledge of TNBC biomarkers, would provide an opportunity to introduce targeted monotherapy, which would be able to reduce the use of toxic chemotherapy [24].

CONCLUSION

TNBC is a difficult-to-treat malignancy characterized by poor endocrine function, which limits the choice of therapeutic options. Surgery and systemic chemotherapy, which causes many side effects, remain the primary treatment options. The lack of good alternatives has prompted researchers to study more effective and less toxic therapies. So far, clinical trials have been conducted on the use of immunotherapy both in mono- and polytherapy. An interesting and promising direction is molecular targeted therapy, which offers hopes of tailoring treatment and reducing the harm of other old methods.

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