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Overcome the invisible – new treatment opportunities for triple negative breast cancer

Ewelina Jałonicka[1], Maksymilian Sikorski[2], Grażyna Gromadzka[3]

[1] Immunis Scientific Club, WM.CM.UKSW, Faculty of Medicine. Collegium Medicum, Cardinal Stefan Wyszyński University in Warsaw

[2] Immunis Scientific Club, WM.CM.UKSW, Faculty of Medicine. Collegium Medicum, Cardinal Stefan Wyszyński University in Warsaw

[3] Immunis Scientific Club, WM.CM.UKSW, Faculty of Medicine. Collegium Medicum, Cardinal Stefan Wyszyński University in Warsaw

ABSTRACT

Breast cancer is considered a disease of civilization. It is diagnosed in approximately 1.7 million women each year, and more than 500,000 people die. Among the diagnosed neoplasms, 15-20% are TNBC (triple negative breast cancer) characterized by weak expression of estrogen and progesterone receptors and overexpression of the human epidermal growth factor 2 receptor. TNBC is a very heterogeneous group cancers. TNBCs are considered aggressive as they are usually diagnosed at higher stages, often appear in younger patients, and develop faster than some other breast cancers. Moreover, when these tumors do not respond to chemotherapy in the early stages, they have a great tendency to spread to other parts of the body. The aim of the study is to present data on the modern application of immunotherapy in the treatment of patients with triple negative breast cancer. The topics of effectiveness and the mechanism of action were discussed. The latest scientific reports have been taken into account.

Inhibition of ICI (immune checkpoint) is a new and effective method of treatment in several types of solid tumors. Unfortunately, for TNBC, the use of monotherapy targeting PD-1, PD-L1 or CTLA-4 showed little effect. Still many types of immunotherapy are questionable as to their effectiveness. However, in 2019 The Food and Drug Administration (FDA) has approved the use of atezolizumab in combination with the protein – paclitaxel in the treatment of adult patients with inoperable, locally advanced TNBC. Results from a multicentre randomized trial of 902 patients showed a higher median PFS (progressive-free survival) in patients receiving atezolizumab with paclitaxel. The PFS was 7.4 months in patients receiving atezolizumab plus paclitaxel protein-bound and 4.8 months in patients receiving placebo plus paclitaxel protein. ORR (objective response rate) was 53% and 33%, respectively. Unfortunately, in the 2022, a case report was reported describing the adverse reaction of sarcoidosis caused by atezolizumab in a patient with metastatic breast cancer. It turns out, therefore, that while immunotherapy is a hope for TNBC patients, it is not free from undesirable side effects.

The work is of a review character. A review of the scientific literature was made using the PubMed NCBI database and other sources and materials related to the topic of the work.

Keywords: TNBC, breast cancer, immunotherapy

THE AIM OF THE STUDY

The aim of the study is to present new possibilities of treating triple negative breast cancer (TNBC). This type of cancer is discussed in this paper. Issues such as TNBC immunotherapy, immune checkpoint inhibitors (ICI), the use of combined therapy with atezolimumab with paclitaxel or the case of adverse reaction after atezolimumab were also addressed. The targets of TNBC immunotherapy have been given particular attention. The knowledge of immuno-oncology may translate into the development of effective and relatively safe therapies for patients.

The aim of the study is to present new treatment options for triple-negative breast cancer (TNBC). This type of cancer is discussed in this article. Issues such as TNBC immunotherapy, immune checkpoint inhibitors (ICI), the use of therapy with atezolimumab in combination with paclitaxel, or an adverse events after atezolimumab were also discussed. Particular attention has been paid to the goals of TNBC immunotherapy. Knowledge of immuno-oncology may translate into the development of effective and relatively safe therapies for patients.

METHODOLOGY

The review of the scientific literature was carried out using the PubMed NCBI database (National Center of Biotechnological Information) and other sources and materials related to the topic of work, directly or indirectly. The search in the PubMed NCBI database was carried out by entering phrases such as TNBC, Cancer ICI, ICI TNBC, Atezolizumab and Nab-Paclitaxel, hypoxic tumor, cd73 tnbc, cancer lncRNA, microsatellite instability, YAP signaling PD-L1, Wnt singaling cancer, miR-135, PD-1 (AND) TNBC, CTLA-4 (AND) TNBC, next generation immune modulatory (AND) TNBC, TNBC. The date of publication restriction was applied during the search – papers published in the last 10 years were preferentially selected.

BREAST CANCER

The brest cancer is the most common malignant neoplasm in women (about 15% of cancer cases and 15% of cancer deaths worldwide). In the world, including Poland, mortality from breast cancer is decreasing , which is related to the improvement of diagnostic techniques and treatment methods.

In the initial stage, breast cancer is asymptomatic, and the most common visible symptom is a single tumor, which is homogeneous, squamous and not sharply demarcated from other tissues. Imaging techniques such as mammography, ultrasound and magnetic resonance imaging are used in diagnostics. Among the microscopic techniques, there are histopathological and cytological examinations. According to the World Health Organization, there are infiltrating and non-infiltrating tumors. The former, in turn, are divided into infiltrating without a type specification (NST, without a special type), formerly ductal, lobular and special forms. The latter are divided into lobular in situ and intraductal (ductal in situ) (Jassem, 2019).

It is estimated that breast cancer is diagnosed in approximately 12% of women in the United States. In 2017, 25,000 cases of breast cancer were diagnosed in the US. There are 3 main types of breast cancer: hormone receptor positive/ ERBB2 negative (70% of patients), ERBB2 positive (15-20%), and triple-negative (15%). The latter has the worst prognosis of all types of breast cancer. It does not have standard molecular markers.

Median survival for metastatic TNBC is approximately 1 year. For comparison, for the other two subtypes of breast cancer it is 5 years (Waks, 2019).

In recent years, new drugs have been developed that are molecules that antagonize the immune checkpoints, including CTLA-4 (cytotoxic T cell antigen 4), PD-1 (programmed death receptor 1) or PD-L1 (programmed death ligand 1). They significantly influenced the effectiveness of the treatment of many cancers. Recently, they have been used in the treatment of breast cancer (Emens, 2018).

It turns out that the response of TNBC patients to the use of these drugs may be positive and long-term, and the application of this therapeutic strategy is one of the new potential therapeutic solutions. This topic will be discussed in the following sections of this chapter.

TNBC

TNBC accounts for approximately 15-20% of breast cancers. This neoplasm is characterized by an unfavorable clinical course and a poor prognosis. Histologically, such a neoplasm is characterized by a lack of steroid receptors (estrogen and progesterone) and an overexpression of the human epidermal factor type 2 receptor (HER-2). The presence of receptors is tested by immunohistochemical methods using fluorescence in situ hybridization (FISH). Treatment usually includes surgery and chemotherapy as systemic treatment. The problem is, among others however, there are no known specific treatment targets for TNBC. However, efforts are still being made to find targeted therapy (Ryś-Brynarska, 2021).

Among others, poly-ADP-ribose polymerase (PARP), which can bring positive medical results, is increasingly used. Translating research to the clinic is difficult, for example due to the fact that TNBC is a molecularly diverse tumor (differences between the outside and inside of the tumor) (Vagia, 2020).

TNBC is a cancer with a high relapse rate. This is especially true for the first 3 years. The risk of relapse drops sharply after 5 years. The cells of this tumor are characterized by rapid proliferation. An example of a new immunotherapy-based treatment is is the combination of atezolimumab and nab-paclitaxel approved by the Food and Drug Administration (FDA) (Singh, 2021).

IMMUNOTHERAPY IN TNBC

Specifically, TNBC immunotherapy targets include PD-1/ PD-L1 Axis, CTLA-4, and Dual Checkpoint Inhibition, as well as next-generation immunomodulatory targets. The breakthrough in the treatment of melanoma has contributed to the development of immunotherapy in this type of cancer. It is difficult to find specific treatment goals in TNBC, which is why immunotherapy seems to be a good idea (Mediratta, 2021).

PD–1/PD-L1 AXIS

The interaction between programmed death ligand 1 (PD-L1) with programmed death-1 receptor (PD-1) is necessary to escape the host immune system. High PD-L1 expression is a predictor of poor prognosis, although positive PD-L1 tumors respond better to treatment with immune checkpoint inhibitors. In TNBC, 50% of tumors are characterized by lymphocyte infiltration in the tumor core or stroma. Such a histological structure indicates a better prognosis and a better response to treatment (Majidpoor, 2021).

Quin et al. checked whether TNBC has a higher PD-L1 expression than other breast cancer subtypes. PD-L1 expression was shown by 61.5% of TNBC tumors and 18.6% of non-TNBC cancer subtypes. Thus, TNBC has been shown to have higher PD-L1 expression. Additionally, TNBC tumors larger than 20 mm showed higher PD-L1 expression. Researchers also found nucleophosmin (NPM1) specifically binds to the PD-L1 promoter in TNBC cells and activates transcription of the PD-L1 gene and thus inhibits T-cell activity. Study results indicated that NPM1 is a regulator of PD-L1 transcription in TNBC. This may positively translate into the development of new strategies to increase the effectiveness of TNBC immunotherapy. In addition, the study also showed that PARP1 inhibits PD-L1 transcription by binding to the NPM1 nucleic acid binding domain of the PD-L1 promoter. Olaparib, a PARP inhibitor, increases PD-L1 expression in TNBC, which is important for better efficacy of anti-PD-L1 therapy (Qin, 2020).

Kong et al. identified the cell surface CD44 receptor as a key regulator of PD-L1 expression in TNBC and in non-small cell lung cancer. CD44 activated PD-L1 transcription with the involvement of i.a. cleaved intracytoplasmic domain. Research results indicate that CD44 may be a new therapeutic target useful in suppressing the intrinsic function of PD-L1 tumor (Kong, 2020).

CTLA-4 AND DUAL CHECKPOINT INHIBITION

It turns out that there are complementary mechanisms of TNBC's double checkpoint blockade. According to the study results, the combination of anti-PD1 and anti-CTLA4 significantly increased the effectiveness of both therapies. This probably has to do with the fact that anti-CTLA4 increases the expansion of the T-cell receptor (TCR). This combination also activates a daptive anti-tumor immunity in triple-negative breast tumors (Singh, 2021).

NEXT GENERATION IMMUNE MODULATORY DRUGS

The use of immune checkpoint inhibitors is beneficial, but not for all patients. It is important to identify a group of patients in whom such treatment may be the most effective. Wu et al. conducted an analysis the results of which indicate the potential use of a combination of information on CD8, PD-L1 expression and somatic mutations to make decisions about clinical management and treatment (Wu, 2022).

In a study by Ahn et al. TNBC-positive PDL1 tumors were found to be characterized by lymphocytic infiltration. These tumors have relatively good survival rate. This is state on the basis of SP142 test. In the SP142 test, PD-L1 positive tumors also showed the presence of greater numer of CD8 + T cells. The relapse-free survival rate was also higher for the PD-L1 positive tumor (Ahn, 2021).

Not only immunotherapy based on PD1-PDL1 axis blockade may bring therapeutic benefits. Much preliminary research on other immunotherapies has shown promising results. Potential solutions may also be related to the agonism of costimulatory molecules, the interstitial administration of immunotherapy or anti-cancer vaccines. It also seems important to conduct further research on subsequent checkpoint inhibitors. Knowing for which patients which type of immunotherapy will benefit treatment may be useful, therefore it is important to identify and test immunological biomarkers (Tarantino, 2022).

INHIBITION ICI

Immunity checkpoints are part of the regulation of immune system function that protects healthy cells from damage. The mechanism of the action of immune checkpoints is based on the presence of specific proteins on the surface of cells that can be recognized by T cells, thereby suppressing the immune response by these cells. Immune checkpoint inhibitors (ICIs) block these proteins, allowing T cells to kill cancer cells (https://www.cancer.gov/about-cancer/treatment/

types/immunotherapy/checkpoint-inhibitors).

ICI can be used to treat TNBC. One possible treatment option is based on the use of anti-PD-1 or anti-PD-L1 monoclonal antibodies. The tumor-infiltrated lymphocytes express the PD-1 receptor and the tumor cells express the PD-L1 programmed death ligand. This interaction is known as the immune checkpoint. This immune checkpoint is blocked by the antibodies indicated above, which promotes anti-tumor immunity (Lipson, 2015). Pembrolizumab and Atezolizumab, respectively, are examples of investigated and tested antibodies to molecules involved in suppressing the anti-tumor T cell response by a mechanism involving immune checkpoints. (A Study of Atezolizumab (an Engineered Anti-Programmed Death-Ligand 1 [PDL1] Antibody) to Evaluate Safety, Tolerability and Pharmacokinetics in Participants With Locally Advanced or Metastatic Solid Tumors; Study of Pembrolizumab (MK-3475) Monotherapy for Metastatic Triple-Negative Breast Cancer). Only a small part of the patient population benefited from monotherapy with anti-PD-1 / anti-PD-L1 antibodies and such treatment did not bring better outcomes than chemotherapy (Vonderheide, 2017). Additionally, it was observed that such treatment caused a neuro-toxic effect (Vilariño, 2020). The cytotoxic T-cell protein 4 (CTLA-4) is another well-researched mechanism of ICI that can be used in the treatment of TNBC. It is a receptor expressed on Treg lymphocytes and elevated on the surface of Th and Tc lymphocytes, which inhibits the activity of potential autoreactive T lymphocytes (Krummey, 2020). Anti-CTLA-4 antibodies have the same effect as anti-PD-L1 / PD-1 antibodies in that they allow T cells to remain active and exhibit anti-tumor activity. Unfortunately, anti-CTLA-4 monotherapy and the combination of both methods did not have a beneficial therapeutic effect and increased the likelihood of autoimmune diseases (Liu, 2020). While these techniques on their own have not been effective enough, they are nevertheless quite promising.

Research is exploring the possibility of combining ICI monotherapy with other antibo-dies, such as anti-OX40 and chemoterapeutic drugs, for better outcomes. The effectiveness of ICI treatment may be influenced by various factors, such as: tumor dysregulated vascularization, expression of interleukin-8 and CXCR1 / CXCR2, CD73, long non-coding RNA (IncRNA), microsatellite instability (MSI), WNT and YAP signaling pathways, nanoparticle platforms (Mediratta, 2021).

DYSREGULATED TUMOR VASCULATURE

Over time, tumor cells can become extremely hypoxic and endothelial cells may migrate to the tumor core due to increased expression of the angiogenic growth factor. All this inhibits drug entry, lowers T cell activation, and increases PD-L1 expression through INFγ (Schmittnaegel, 2017; Kammertoens, 2017). Combining ICI with anti-angiogenesis therapy may improve the treatment of TNBC. One of the options available is to use a certain class of peptides, for example AXT201. It inhibits VEGF, HGF, IGF1 and some studies indicate that it contributes to the decrease in the number of cells expressing PD-L1 and may also inhibit the pro-angiogenic effect of INFγ (Mirando, 2020).

Additionally, the state of hypoxia can be reversed with the use of oxygen microcapsules, which, in combination with anti-PD-1 antibodies, may increase infiltration of CD45+ cells in the tumor microenvironment (Wu, 2022).

INTERLEUKIN-8 AND CXCR1/CXCR2

Both of them have been shown to be overexpressed in numerous malignant neoplasms, including breast cancer (Cheng, 2019) They bind, changing the status from epithelial to mesenchymal, which promotes migration, invasion, and the regrowth of secondary tumors (Fernando, 2011) The use of IL-8 inhibitors and antibodies anti-CXRC2 may exert anti-tumor activity. Additionally, IL-8 can be used as a biomarker of the benefits of ICI therapy (Sanmamed, 2017).

CD73 EXPRESSION

CD73 converts extracellular AMP to adenosine, which prevents an excessive immune response. CD73 expression is induced in tumors, which contributes to the production of adenosine excess, that inhibits effector T cells by binding to A2A receptors (Sciarra, 2019). In TNBC, adenosine may protect cancer cells from an anti-tumor response and promote cell migration and invasion. Additionally, inhibition of CD73 through APCP reduces cell migration and the EMT proces (Petruk, 2021; Takedachi, 2008). Treatment with a combination of anti-CD73 and anti-PD-1 antibodies shows encouraging results [32].

LONG NON-CODING RNAS

Numerous studies have shown that lncRNAs contribute to resistance to cancer treatment. Additionally, one of the classes of lncRNA – circular RNAs, can act as miRNAs sponges. Multiple circRNA have been identified in TNBC that increase proliferation rates (circGFRA1) and promote epithelial-to-mesenchymal transition (circANKS1B). Moreover, hsa_circ_0072309 has been identified as a potential TNBC risk factor (Magalhães, 2022). However, targeting lncRNAs in therapy is challenging. Combinatorial treatment requires further research (Yan, 2019).

MICROSATELLITE INSTABILITY (MSI)

Microsatellites are short repeated sequences in the genome, that result from the mal-function of DNA repair systems. High MSI status can be associated with patient's senistization to ICIs (Le, 2017). Patients with higher MSI status are more likely to express PD-L1, so, it is also used as a biomarker. The analysis of the MSI status can potentialy help in finding the best treatment (Yoshida, 2022).

WNT AND YAP SIGNALING PATHWAYS

Wnt/β-catenin signaling pathway is associated with the epithelial-mesenchymaln transition (EMT). Activation of this pathway stimulates cell proliferation and has been linked to several cancers, including breast cancer (Jiang, 2019). Moreover, Wnt inhibitors decrease PD-L1 expression, while Wnt agonists increase it. As a result, inhibitors can be used in conjunction with ICIs to improve treatment outcomes (Castagnoli, 2019). One potential candidate for combination therapy may be miR-135. Its overexpression in breast cancer has been shown to reduce cell proliferation, migration, invasion, and metastatic spread. Additionally, it increases the expression of E-cadherin and decreases expression of Snail, Slug, neural-cadherin, Vimentin, which means slowing down EMT. All this is achieved by inhibiting, at least in part, the Wnt/β-catenin signaling pathway (Maeda, 2018).

YAP signaling enhances PD-L1 expression and mediates suppression by regulating T cells [38]. They recruit many cell types such as tumor-associated macrophages by initiating the expression of cytokines and chemokines. An example of the application of this information in practical studies is the combination therapy of ICI with the YAP inhibitor verteporfin, which gave better results than monotherapy with ICI (Yu, 2021).

NANOPARTICLE PLATFORMS

They can be used as an ICI delivery system instead of monoclonal antibodies, that can stimulate self-reactive T cells. Additionally, this approach supports the pharmacokinetics and pharmacodynamics of combinatorial therapies (Gurunathan, 2018).

ATEZOLIMUMAB WITH PACLITAXEL

Atezolizumab attacks PD-L1 present on tumor-infiltrating immune cells by preventing its interaction with PD-1 receptors. Atezolizumab is an example of an ICI. It has been approved as a drug in the treatment of metastatic urothelial carcinoma and non-small cell lung cancer, but it also shows good results in TNBC (Tecentriq (atezolizumab): summary of product characteristics; Emens, 2019) ICI can improve the response to chemotherapy, for example taxanes such as (nab)-paclitaxel. The combination of Atezolizumab and Nab-Paclitaxel used in the study extented progression-free survival (PFS) with TNBC (A Study of Atezolizumab in Combination With Nab-Paclitaxel Compared With Placebo With Nab-Paclitaxel for Participants With Previously Untreated Metastatic Triple-Negative Breast Cancer).

PFS was significantly longer in the atezolizumab plus nab-paclitaxel treatment group (7.2 months) compared to the placebo plus nab-paclitaxel treatment (5.5 months). This was particulary notable in PD-L1-positive group, where atezolizumab-nab-paclitaxel PFS was 7.5 months and placebo-nab-paclitaxel was 5.0 months. Moreover, the objective response rate was much higher: 58.9% vs. 42.6%. The adverse events were identical in both groups, with alopecia being by far the most common. Both groups had equal levels of safety (Jotte, 2020).

This study confirmed the value of including ICI in the first-line treatment of metastatic TNBC

(Schmidt, 2018). Further approval of the drug is dependent on additional studies, showing that treatment has not reached its original PFS value. The FDA reassessed the need for rapid approval, despite the fact that the Oncology Drugs Advisory Committee (ODAC) decided to maintain the accelerated approval of atezolizumab in April 2021 (https://www.cancernetwork.com/view/atezolizumab-tnbc-indication-withdrawn-by-manufacturer-after-talks-with-fda).

CASE REPORT – ADVERSE REACTION AFTER ATEZOLIMUMAB

Immunotherapy is believed to have revolutionized the way cancer is treated. However, be aware that it can also be associated with side effects. An example would be tumor-related sarcoidosis-like reactions (SLR). According to the data, this problem affects 4.4% of malignant tumors. May be related to immunotherapy. However, the exact determination of the cause may be difficult, as it cannot be ruled out that the occurrence of SLR is related to the patient taking other medications (along with immunotherapy). It has been suggested that the efficacy and safety of immunotherapy may be influenced by the use of various medications. Among them there are antimicrobial agents, proton pump inhibitors and steroids. In this section, we present a specific example (case report) to illustrate the problem that may arise after atezolimumab in combination with nab-paclitaxel in TNBC.

A 50-year-old female patient diagnosed with TNBC was treated with atezolimumab in combination with nab-paclitaxel. However, after 5 cycles, lymph node enlargement in the right armpit and the appearance of a subcutaneous tumor in the limbs were observed. The results of the biopsy of this nodule indicated the formation of epithelial granulation tissue with giant Langhans cells. After discontinuation of atezolimumab, the lymph nodes and subcutaneous mass decreased. Let us add that the patient's medical history did not include the use of drugs (mentioned above) that could potentially affect the course of immunotherapy treatment, hence it can be concluded that SLR was related to the use of atezolimumab.

It seems appropriate to thoroughly investigate SLR as a side effect of immunotherapy (Tsunoda, 2022).

SUMMARY

TNBC accounts for approximately 11% of all new cases of breast cancer, the most common malignancy in women. Faced with poor treatments, new therapeutic approaches need to be developed. Part of this process is finding a new generation of immunomodulatory targets as well as the use of immune checkpoint inhibitors in the PD-1 / PD-L1 or CTLA-4 axis. Most studies show that while they are promising therapies, more work is still needed to refine them, especially in the search for effective combinations of chemotherapy and modulation of the immune response. It also demonstrates the importance of an interdisciplinary approach in medicine and how collaboration between scientists and clinicians can improve treatment outcomes.

CONCLUSIONS

TNBC is one of the worse prognosis neoplasms for which it is difficult to find therapeutic targets that would significantly translate into treatment efficacy. A breakthrough in the treatment of melanoma contributed to the development of TNBC immunotherapy. This seems to be a potentially good idea. The goals of immunotherapy in TNBC include: TNBC immunotherapy targets include: PD-1 / PD-L1 axis, CTLA-4 and Dual Checkpoint Inhibition, as well as next generation immune modulatory targets. More research and solutions are needed to support the response to immunotherapy in TNBC patients. It is also worth noting that they may contribute not only to the effectiveness of TNBC immunotherapy, but may also lead to finding potential snake points for treatment in TNBC. Let’s add that medicine is advancing even in difficult-to-treat diseases such as TNBC, and the results of each study are valuable.

General comments/thanks

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