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Immunotherapy in the Treatment of Triple-negative Breast Cancer: the Impact and Potential of the TME

Shuoming Chen, Sihan Zhou[2,] *

[1] Guangdong country garden school Foshan, Foshan, Guangdong, 528000 China
[2] College of Animal Science, South China Agricultural University, Guangzhou, Guandong, 510642, China
*Corresponding author: 202219110233@stu.scau.edu.cn

Abstract:

Triple-Negative Breast Cancer (TNBC) is considered to be the most immunized breast cancer subtype. Compared with other types of breast cancer, it has higher invasion and poor prognosis, accounting for about accounting All breast cancer is 15%to 20%. And TNBC's tumor-infiltrating lymphocytes (TILS) number, programmed cell death-ligand 1(PD-L1) expression level and tumor mutation burgen (TMB), These indicators are higher than other subtype breast cancer, and it is prompted that TNBC's Tumor Microenvironment (TME) has strong immune activity, which provides a certain foundation for immunotherapy in the application and promotion of immunotherapy in TNBC. Immunotherapy provides TNBC with a new treatment strategy by activating and attacking tumor cells by activating the patient's own immune system. The immunotherapy of TNBC is roughly divided into: immune checkpoint inhibitors (ICIs), adoptive cell transfer therapy (ACT), Cancer Vaccines (CVS), and oncolytic virus (OVS). The treatment of immunotherapy on TNBC is of great significance. For this reason, this article further explores how the four major immunotherapies can identify and attack tumor cells by activating the patient's own immune system. Whether the therapy is effective for TNBC patients, put forward new possibilities for treatment and pave the way for subsequent researchers' experiments. This study will provide new insights and directions for TNBC's treatment.

Keywords: TNBC; ICIs; TME; PD-1/PD-L1.

1. Introduction

From the above, serious challenges in the TNBC therapy arise, because the absence of expression of the oestrogen, progesterone, and ERBB2 receptors, respectively, forms this type difficult to treat through the conventional approaches followed in treating other breast cancers. The absence of these has led to the poor response of TNBC to the majority of the therapy, including those developed and mostly useful for other breast cancers in subcategories, such as hormone and human epidermal growth factor receptor 2 (HER2)-targeted therapies. This left the option of cytotoxic chemotherapy to a physician for years, despite having limited effectiveness, knowing that patients with TNBC have been treated with cytotoxic chemotherapy after many years of receiving chemotherapy. high relapse rates in TNBC patients following chemotherapy [1].

TNBC presents with very poor prognoses, much more likely to metastasize early, and with a shorter survival time after recurrence than patients with other subtypes of breast cancer. The mainstay of treatment in the early stages consists of anthracycline- and paclitaxel-based chemotherapy. Although the addition of platinum-based agents to standard therapy remains controversial, as no clear added value in survival could be demonstrated, adjuvant capecitabine emerged for patients with TNBC and residual disease post-chemotherapy. Management of early-stage TNBC in this present day has indicated some promising results beyond the traditional options of treating with cytotoxic drugs through the use of poly ADP-ribose polymerase (PARP) inhibitors and combination with immunotherapy and chemotherapy [2].

This, therefore, shows that TNBC, with its characteristics of being heterogeneous and aggressive, has complexity that would not only require therapeutic strategies but this level would need them. Despite these challenges, developments in the comprehension of molecular subtypes and genetic signatures of TNBC have defined new therapeutic opportunities; with such advances, it has apparently paved the way for changes toward more individualized TNBC treatments and draw on the peculiar molecular traits of the TNBC tumors [2].

In general, while TNBC is clearly non-responsive to conventional breast cancer treatment, its nature and possible

treatment modulation is pursued, and hence, research on TNBC has to continue. This still offers a ray of hope for mankind to find some way to tackle this particular cancer type. These include immunotherapy and PARP inhibitors—just some of the new agents that could change the game for this terrible-to-treat subtype of breast cancer.

2. The Mechanism and Results of Immunotherapy for TNBC

This is an approach that has significantly led to the development of ICIs for immunotherapy towards the treatment of clinical tumors. Prime targets under research of ICIs remain PD-1, PD-L1, and CTLA-4. The monoclonal antibody PD-1/PD-L1 and CTLA-4 had been effective for negative regulation of antitumor T cell activation in tumor cells and TME.

2.1 ICIs

2.1.1 PD-1/PD-L1 inhibitors

These expressed PD-L1 molecules on the surface of the tumor cells may, therefore, overcome the host immune T cell-mediated surveillance by binding to PD-1 molecules on the T cells. On the other hand, above the anti-PD-L1 function, anti-PD-1 and anti-PD-L1 blocking antibodies abrogate the above effects, enhancing the proliferation function of T-cells and killing cells for antitumor effects [3].

The PD-1 pembrolizumab-monoclonal antibody, associated with a range of major low-grade toxic effects in its first-line patients with metastatic TNBC, showed antitumor activity. These included researches on breast cancer as part of the KEYNOTE series and researches on non-small cell lung cancer and gastric cancers from other solid tumors conducted by KEYTRUDA. The KEYNOTE is a series of studies that included the above-discussed KEYNOTE-173 and KEYNOTE-522, which together have proven the benefit from its application among patients with TNBC in combinations with chemotherapy regimens [4].

These are the preliminary results of the antitumour activity among patients with locally advanced triple-negative breast cancer, without a high signal of severe toxic effects, from the KEYNOTE-173 Phase 1b study, examining pembrolizumab in combination with neoadjuvant chemotherapy. Sixty percent of the patients achieved complete remission pathologically (90% CI 30-85). The study concluded that with neoadjuvant chemotherapy alone, a higher fraction of patients attains pathologic complete remission than would statistically be likely. The phase 3 study of KEYNOTE-522 randomized 1,174 patients with stage II/III TNBC to receive either neoadjuvant pembrolizumab chemotherapy or neoadjuvant placebo chemotherapy, followed by adjuvant pembrolizumab or placebo in the treatment of early-stage TNBC[5].

Two phase 1/II studies—KEYNOTE-012 and KEYNOTE-086—suggested that due to better activity, single-agent Pembrolizumab has better safety in advanced TNBC than the combinations studied above. These were results that formed the basis of the use of single-agent Pembrolizumab in metastatic TNBC treatment in the KEYNOTE-119 phase III study. However, the outcomes reported that it did not significantly improve the OS of single-agent Pembrolizumab compared to that of single-agent chemotherapy (9.9 months vs. 10.8 months) [3]. In conclusion, PD-1 combination therapy is more effective in TNBC patients than PD-1 monotherapy.

2.1.2 CTLA-4 inhibitors

Among CTLA-4 inhibitors, ipilimumab and tremelizum are the most important with respect to clinical therapy. Following its evaluation in several controlled and open-label randomized clinical trials with encouraging results in patients diagnosed with metastatic melanoma, the first immune checkpoint inhibitor that was approved for clinical application was ipilimumab, a fully human IgG1 monoclon chain monoclonal immunoglobulin antibody against CTLA-4, originating from Bristol-Myers Squibb. Its mechanism of spatial blockade is CTLA-4 interaction with CD80/CD86, precluding CTLA-4 from performing its action of inhibition. This blockade allows free binding to CD28 with CD80/86, which stimulates T-cells. Tremelimumab is a human IgG2 monoclonural antibody against CTLA-4. It then binds to CD80/CD86, blocking the interaction with CTLA-4 and thus inhibiting the CTLA-4 pathway. It reverses the deficiency of signaling in T cells and raises the number of effector T cells that are activated, allowing improved attack by immunity on tumor cells.

The safety and efficacy of Tremelimumab in patients with different types of advanced solid tumors were defined through a phase II clinical trial. Objective remmission rate (ORR) was 8.3% (95% CI, 0.2-38.5%), and the median duration of remmission (mDOR) was 12.9 months. The disease control rate (DCR) by the twelfth month was 8.3%. The median progression-free survival (mPFS) was 3.58 months, and the median overall survival (mOS). The current study shows, therefore, that tremelimumab can be administered in patients with TNBC[6].

In medicine, this combination therapy has promised since it will carry benefits from CTLA-4 and PD-1/PD-L1 monotherapy. Anti-PD-1 antibodies block the binding of PD-1 with PD-L1 on the surface of a T-lymphocyte, thus not killing the tumor. The suggested mechanisms of action in animal models and clinical settings of combi-

nation therapy include a reduction in Treg cells; that is, regulatory cells in mouse models of breast cancer. In this line, a significant increase in mice of NK and CD8+ T cell numbers was observed in the case of combination therapy. Even post-treatment discontinuation, T cells stayed markedly highly activated. It was in line with previous findings that anti-CTLA-4, anti-PD-1, or DT modulation enhanced the anti-tumor immune response by suppressing Tregs and activating lymphocytes in a mouse model of breast cancer[6,7].

KEYNOTE important effective series of trials PD-1/PD-L1 inhibitors, either in monotherapy or combination treatment, in early and late TNBC, particularly among the category of patients showing TNBC positivity. On the other hand, combination therapy with CTLA-4 inhibitors is needed only in using the combination of drugs and is not as efficacious as PD-1/PDL1 inhibitors. Both inhibitors show that there is a big difference in their efficacy for patients that are TNBC-positive. This fact, therefore, calls for continuous research for maintaining the hope for TNBC patients who might not derive significant effects while using PD-1/PDL-1 inhibitors.

2.2 ACT

TILs get taken out from patient tumors, and T cells that might target special tumor markers from the blood get picked. These cells are then grown big in the lab and put back into the patient through a vein. Before this, treatments like cyclophosphamide or full-body radiation cut down Tregs in the body, making ACT work better.

ACT sometimes means putting new TCR or CAR into T cells to hit only tumor cells. TCR-T therapy has T cells spot antigens with help from MHC. CAR-T cells, though, spot tumor cell surface markers without needing MHC[8,9].

This has been tried on many solid tumors, including TNBC, looking at how safe and workable it is. Study info shows, in a CAR-T study on ROR1 (a marker found in breast and lung cancers), 4 patients saw some tumors shrink. Another study mixed lymphodepletion, intrathoracic delivery, and Pembrolizumab. Out of 27 patients, one with breast cancer, about 56% saw no disease growth; 12.5% saw tumor shrinkage. In a TCR-T study, 2 out of 17 breast cancer patients showed disease reduction after getting MAGE-A3, lymphodepletion, and high-dose IL-2. About 5.9% had no more detectable disease; 17.6% saw some improvement,A study (trial number NCT01967823) with nine participants noted an objective response (partial response) in one breast cancer patient following lymphocyte depletion [10].

In summary, using ACT for TNBC needs more study before it can be a regular treatment. Even though it's promising, especially for melanoma and some blood cancers, there are hurdles like picking the right immune cells, keeping them alive and active after putting them back in the body. ACT might be an option later to swap out treatments like chemo or ICIs for hard-to-treat patients.

2.3 CVs

CVs are one of the anti-tumour active immunotherapy modalities, which are based on the principle of introducing tumour antigens into the patient‘s body to activate or enhance the body‘s immune system and generate an effective anti-tumour immune response, thereby killing or clearing tumour cells [11]. Based on their structure and substance, cancer vaccines fall into three basic categories: cellular vaccines (made of immune or tumor cells), protein/peptide vaccines, and nucleic acid vaccines (made of DNA, RNA, or viral vectors)[12]. TNBC vaccines currently in clinical studies include NeuVax, Adagloxad Simolenin vaccine, and α-lactalbumin vaccine [3].

After standard therapy was finished, disease-free patients were included in a phase IIb, multicenter, randomised, single-blind, controlled trial to test NeuVax, a peptide vaccine derived from HER2. (NCT01570036). After receiving trastuzumab monotherapy for a year, patients were randomized to receive either nelipepimut-S (NPS) in conjunction with GM-CSF or a placebo group (GM-CSF, control). Out of the 275 patients who were randomly assigned, 136 received NPS with GM-CSF and 139 received a placebo with GM-CSF. There was no discernible change in the estimated DFS between the NPS and control groups at a median follow-up of 25.7 months (interquartile range, 18.4-32.7) [HR, 0.62; 95% CI, 0.31-1.25 ; P = 0.18].It was safe to combine NPS with trastuzumab monotherapy. There was a significant clinical advantage seen in TNBC patients, however there was no significant difference in DFS in HER2 low-expressing breast cancer according to the intention-to-treat study[13].

The scientists created vaccines with HER2-derived peptides, such as (NPS), which functions as an immunological adjuvant by binding to GM-CSF. A Phase II trial demonstrating a substantial improvement in DFS in vaccinated patients compared to unvaccinated controls was prompted by promising preliminary clinical work with this CD8+ T-cell generating vaccine. These findings led to the initiation of the phase III PRESENT study, wherein patients with HER2 1+ or 2+ breast cancer and positive lymph nodes were randomly assigned to receive GM-CSF with NPS or GM-CSF alone. The experiment was ended as ineffective since there was no vaccination benefit when an interim analysis was scheduled [13].

Findings from a number of preclinical investigations indicate that when T cells are activated, CVs also increase

the expression levels of cell surface inhibitory receptors. One possible mechanism is that, initially to prevent the in vivo immune response from being overamplification, increasing IFN-γ secreted by tumor-specific T cells proportionately upregulates PD-L1 expression on cancer cells and antigen-presenting cells (APCs). Combining immune checkpoint blockades (ICBs) with breast cancer vaccines is a potential approach that could improve and extend the immune response and ultimately yield major therapeutic effects [14].

In summary, breast cancer vaccines have not provided significant clinical benefit in the last two decades, and only a few breast cancer vaccines have entered phase III clinical trials, and unfortunately, most of these trials have failed. In order to improve the effectiveness of TNBC vaccines, researchers have turned to the combined treatment strategy of vaccines and ICB [3,12].

2.4 OVs

The host selectively permits the OV to infect and lyse cancer cells, allowing the induction of the immune systems of hosts against the tumors. In this aspect, therefore, OVs come in handy with an essential role in treating TNBC, since OVs can directly kill tumor cells and, therefore, can activate the immune response. Thus, the most relevant targeting of EEPHB4/EFNB2 signaling in TNBC will be with lack of efficacy in molecularly targeted therapeutic options for TNBC [15]. In fact, from within those therapeutic studies with OVs designed for TNBC in which some (like modified adenoviruses (OAds)), there is the evocation of a strong antitumor immune response that brings forth the immune death of the tumour cells.

As an example, ads with highly specific targets in TNBC have shown very significant anti-junoma activities in preclinical models and have proved safe with potential efficacy seen in their early clinical trials [16]. Despite being a great promise for efficacy against TNBC, OVs show many difficulties that remain both within scientific research and clinical practice. This will include selectivity in targeting the virus, regulated induction of the immune response from treatment, and low side effects upon normal tissues.

Moreover, combined approaches to employing other therapeutic regimens include ICIs which have come into research to enhance the effectiveness of the treatment [17]. On the other hand, one of the very broad potential applications with the development of genetic engineering and molecular biology technologies for the treatment of TNBC is oncolytic virus therapy. Continued research will find the best combination therapies; however, OVs will be more efficacious and safer. As a result, these come with future clinical trials and research on the field dealing with the long-term efficacy of OV therapy aiming at when the quality of life of the patients starts getting improved on account of such treatments.

3. Conclusion

In the treatment of TNBC patients, due to the lack of treatment targets, it has not been effective. This article lists the four major therapies of ICIS, ACT, CVS, and OVS therapy and clinical analysis of the treatment efficacy of TNBC patients. PD-1/PDL-1 inhibitors and CTLA-4 inhibitors have significant effects in the treatment of TNBC patients, and in PD-1 single drug treatment and PD-1 combined treatment, through the KEYNOTE series related PEMBROLIZUMAB PD-1 combination therapy is more effective than single drug treatment. The trials of clinical clinicals in ACT and tumor vaccine and tumor virus therapy are still very lacking. In the early exploration stage, it is still necessary to study. Among them, ACT‘s CAR-T therapy and TCR-T therapy, the trials of CAR-T cell therapy for ROR1 and MESOTHELIN, as well as Mage-A3 tests in TCR-T therapy all reflect that the efficacy of ACT treatment TNBC is not significant, and it still needs to be needed. More clinical research support and demonstration of clinical trials. As well as the clinical trials of tumor vaccine and tumache virus therapy have not brought significant benefits, they will explore joint solutions such as joint treatment with ICIS in the future. As described in this institute, although immunotherapy has made major breakthroughs on TNBC, it is still in the early exploration stage, and any patients are resistant to immunotherapy. In the future The drug tolerance mechanism and seek new treatment strategies to reverse drug resistance.

Authors Contribution

All the authors contributed equally and their names were listed in alphabetical order.

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