Transactions on Materials, Biotechnology and Life Sciences
ISSN: 2960-1932, eISSN: 2960-2319 | Volume 6
FBSE 2024

Immune checkpoint inhibitors for the treatment of Tiple-negative breast cancer

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Abstract. Recently, the use of immune checkpoint inhibitors (ICIs) on triple negative breast cancer have been a hot research topic. immune checkpoints are vital as they prevent an immune response from being so strong that it kills healthy cells, which is unwanted. When T cell surface proteins bind to partner proteins (immune checkpoint proteins) on other cells, for instance tumor cells, immune checkpoints engage. When the checkpoint and immune checkpoint protein bind together, a signal is released to prevent the cancer from being killed by the immune system. ICIs work by stopping checkpoint proteins from binding with partner proteins, so the “off” signal was not sent, allowing the immune system to kill the cancer cells. In this review we will focus of the effect of ICI monotherapy, ICI with chemotherapy and ICI with radiotherapy. Results showed that ICI monotherapy, combination of ICIs and chemotherapy, and combination of ICI and radiotherapy have greatly improved ORR, PIS, and OS compared to the traditional chemotherapy. The combination therapy have also revealed a higher cost-effectiveness compared to ICI monotherapy.

Keywords: Immune checkpoint inhibitors(ICIs); ICI monotherapy; ICI Combination Chemotherapy

1. Introduction

Breast cancer is most usual cancer with high level of death. In 2008 have approximately 1.38 million new case of breast cancer with almost 60% death case happened in the countries which is developing. There is huge difference between developed countries and developing countries. In the developed countries the survival rate is approximately 80% in 5 years. However, in the developed countries is below 40%. Furthermore, in the past 20 years, people have more knowledge about the breast cancer because more relative research about the breast cancer , and bring out the more efficient treatments. In addition, according to the World Health Organization(WHO), the cornerstone of breast cancer management remain improving treatment outcomes and survival rates through early detection. There are different types of medical therapy for breast cancer with antiestrogens such as raloxifene or tamoxifen those could use for treatment of breast cancer and decrease the risk for individual who is possible to have breast cancer. Moreover, for the female who have the high risk of breast cancer, and an additional preventive measure is bilateral breast surgery. For the patient who already been diagnosed can choose from different treatment options. For instance, targeted therapy, radiation therapy, surgery, and chemotherapy. A patient’s quality of life and survival are usually improved by treatment for distant metastases. (1).

There are several different types of breast cancer, first of all it is divided into invasive and non-invasive breast cancers depend on the site.

- Lobular carcinoma in situ (LCIS) this is usually identified as non-invasive breast and develops into breast lobules cancer because it has not extended exterior to the lobular into the breast cancer tissue.
- Ductal carcinoma in situ, it is non-invasive breast cancer, the area is limited to the breast duct
- Infiltrating lobular carcinoma (ILC), it is identified as invasive lobular carcinoma, this types cancer is easily extends to the other place of body and originates in the milk glands
- Infiltrating ductal carcinoma(IDC), it is recognized as invasive ductal carcinoma, and Possibly affecting other parts of the body as well as the breast fatty tissues, IDC originated in the milk ducts of the breast.
- Cancers of the medullary margin separate normal tissue from medullary tissues in invasive breast cancers
- Tubular carcinoma is a type of invasive breast cancer. Woman who have tubular carcinoma are usually more likely to survive than women who have other kinds of invasive cancers of the general kind

Inflammatory breast cancer is rare cancer but grow rapidly and as result of cancer cells blocking lymph channels and vessels in the breast skin, there are dimples or wide ridges. Therefore, it is always appeal in the form of swollen breast which is red and warm(1).

- Paget's disease of breast, it is type rarely happen, usually show the clear change in the nipple and symptoms is red itchy rashes involving nipple and it might spread to the normal skin. Moreover, these types of cancer usually only affect one side of breast
- Phyllodes tumor, it is extremely uncommon and could be either benign or malignant, and cancerous growths of the connective tissues of the breast. However Phyllodes tumor may be removed by surgically.
- Triple- negative breast cancer, there is growing evidence that breast cancer is a heterogeneous disease with specific subtypes that are characterized by different clinicopathological characteristics, prognoses, and treatment outcomes. It is characterized b y inactivation of progesterone receptors, human epidermal growth factor receptors 2 , and estrogen receptors in triple-negative breast cancer

1.1. Treatment for the TNBC

Tiple-negative breast cancer(TNBC) is a specific subtype of breast cancer that does not express estrogen receptor(ER) and progesterone receptor(PR). Furthermore this type of breast cancer have feature of high invasiveness, high metastatic potential and easy to relapse. Because of not sensitive to the therapy of HER2 treatment, and standardized TNBC treatment regimens are still lacking due to do not have ER,PR and HER2 expression. Therefore the investigate new TNBC treatment become the urgent clinic need. (2)

1.2. Current treatment of TNBC

Current the treatment of TNBC is combination therapy, immunotherapy, targeted therapy. TNBC patients cannot receives benefits from existing endocrine drugs or HER2-targeted drugs because of lack relevant receptor markers. As a result, nonspecific chemotherapy remains the standard treatment for TNBC without surgery. The TNBC subtype responds best to taxanes or anthracyclines when used in combination with standard chemotherapy regimens. TNBC is associated with lower complete remission rate and higher mortality rate than non-TNBC subtypes, and less than 30% of patients achieve complete remission. (3)

There are approximately 35%-45% TNBC patients achieve pCR with conventional neoadjuvant chemotherapy in the year 2020. Furthermore, most patients responsive to standard therapeutic option were limited to the nonmetastatic stage. However, the standard therapeutic option did not have the significant contribution to the survival rate.

The standard treatment option is to carry out the chemotherapy and radiation therapy after surgery. In addition, biologically targeted drug therapies target proteins on breast cancer cells that promote their growth, spread and proliferative abilities. (4)

Chemotherapy is major therapy to the patients who diagnosed TNBC due to the ineffective of specific endocrine therapy and targeted therapy. According to National Comprehensive Cancer Network recommendations, paclitaxel, anthracyclines, cyclophosphamide, cisplatin, and fluorouracil should be used in combination. Currently, paclitaxel/docetaxel + doxorubicin + cyclophosphamide (TAC), docetaxel + cyclophosphamide (TC), doxorubicin + cyclophosphamide (AC), cyclophosphamide + methotrexate + fluorouracil (CMF), cyclophosphamide + doxorubicin + fluorouracil (CAF), and cyclophosphamide + epirubicin + fluorouracil + paclitaxel/docetaxel (CEF-T) are the preferred adjuvant treatment options for TNBC. (5)

There are several targeted therapy and potential treatment regimens. However discover new therapeutic targets and perform targeted therapy is extremely hard because of the high heterogeneity of TNBC. TNBC is currently treated with tailored therapies based on immunohistochemical staining results in a large number of clinical trials.

Epidermal growth factor receptor(EGFR)
PARP inhibitors
Androgen receptor(AR)

Estrogen receptor ER-a36
Immunotherapy (5)

2. Immune checkpoint inhibitors for TNBC

Breast cancer immunotherapy has rapid development. Currently, clinical trial arear include t vaccines, antibodies, cytokines, and adoptive cell therapy. The function of Immunotherapy is harness the patient‘s own immune system to specifically attack or kill tumor cells (6)

Currently, there are several breast cancer immunotherapy which is immunotherapy, immune check point blockade and vaccines.

Over the past few years the technology of using immunotherapy have become increasingly mature, and immune checkpoints played a vital role in immunotherapy. There are several types of immune checkpoints, such as PD-1 (Programmed cell death protein 1), PD-L1 (Programmed cell death ligand 1), CTLA-4 (Cytotoxic T lymphocyte associated protein 4) and LAG-3(lymphocyte-activating gene-3). PD-L1 has an essential role in inhibiting immune response and promoting self tolerance by modulating T-cell activity, starting programmed cell death of antigen specific T cells and stopping apoptosis of regulatory T cells. They also functions to reduce the effect of immune response of host cells to the tumour. PD-L1 is a trans-membrane protein and a co-inhibitory factor of the immune response. Its combination with PD-1 reduces the spreading of PD-1 positive cells. [7] CTLA-4 protein is an immune checkpoint molecule, mainly expressed on activating T cells and regulatory Treg cells [9], and is believed to regulate T cell proliferation in lymph nodes[8]. To successfully treat cancer with immunotherapy, the cooperation with immune checkpoint inhibitors are essential. Inhibitors of PD-1 and PD-L1 include Nivolumab, pembrolizumab, JQ1, Atezolizumab, Avelumab, Durvalumab, and Cemiplimab ;inhibitors of CTLA-4 include Ipilimumab; inhibitors of LAG-3 include monoclonal antibody, double antibody and small molecule drug.

2.1. PD-L1 inhibitor and antibodies

Nivolumab is a monoclonal antibody that binds to PD-L1 on the surface of T cells. The principle of how it works is that it prevents the cancer cells from attacking the immune system, so the immune system have the ability to kill the cancer cell. Nivolumab have been approved to be use alone or combined with other drugs to treat diseases like cancer, melanoma, and classic hodgkin lymphoma.

JQ1 is a checkpoint inhibitor which binds with PD-L1. Professor Liu et al and his group discovered that JQ1 can inhibit cell growth and the effect is dependent on dose, which means that a larger dose would lead to a better effect.

Atezolizumab is a human designed anti-PD-L1 monoclonal antibody that blocks the interactions of PD-L1 with its receptors PD-1 and B7.1, enhancing T-cell mediated anticancer immunity.

Avelumab is a human IgG1 monoclonal antibody PD-L1 inhibitor, and is usually is given as an infusion into a vein, usually once every 2 weeks.

2.2. PD-1 antibody and inhibitors

Pembrolizumab works by binding with the PD-1 receptor, helping the immune system to locate the cancer cells so they can be attacked more easily. It also slows or stops the cancer cell from growing and spreading in your body.

Cemiplimab is a human programmed death receptor 1 that binds with PD-1 and inhibits its interaction with PD-L1 and PD-L2. it is often used in metastatic cancer treatment and when other treatment through drugs and radiation is ineffective. The inhibitor showed a safety profile and a high efficacy against metastatic cutaneous squamous cell carcinoma (CSCC) during a clinical trial, but its effectiveness against TNBC were still not proved. Studies of its TNBC therapy are still ongoing and results are not yet available. [13]

2.3. CTLA-4 antibody and inhibitors

Ipilimumab binds to CTLA-4 which prevents the immune system from working properly. When ipilimumab is combined with CTLA-4, your immune system is able to find and destroy the cancer cells. Depending on the patient's treatment plan , the drug is injected into the body through the arm every 3-6 weeks.

2.4. The LAG-3 protein

LAG-3 is a type I transmembrane protein which is structurally similar to CD4. More and more evidences reveals that LAG-3 is an inhibitory coreceptor, playing essential roles in autoimmunity, tumor immunity and anti-infection immunity. [10]

Relatimab is the first LAG-3 inhibitor in the whole world and the third ICI approved in clinical use. Relatimab can bind to LAG-3 receptor to reduce LAG-3 pathway-mediated immunosuppression and promote T-cell proliferation, leading to tumor cell death. [11]

Favezelimab is also a Lag-3 inhibitor,and scientists have been investigating its effect when used with pembrolizumab.

3. ICIs as monotherapy

3.1. Pembrolizumab and TNBC

KEYNOTE-012 was a multicenter and non-randomized phase Ib trial of single agent pembrolizumab given through the vein at 10mg/kg to patients with advanced PD-L1 positive breast, gastric, urothelial, and head/neck cancer. Doctor Rita Nanda, Laura Q, M.Chow and their fellow scientists focused on the effect of pembrolizumab on TNBC here.[12]

In the TNBC cohort, scientists evaluated the safety and antitumor activity of pembrolizumab only in advanced TNBC. 56.3% patient experienced treatment-related toxicity for at least one time, 15.6% experienced at least 1 grade 3-5 event. Pembrolizumab interruption and steroids successfully treated a patient who have drug related aseptic meningitis. The patient showed long lasting PR to pembrolizumab and remained in the study for more than 17 months.[12]

For antitumor activity, 37.5% reported a fall in tumor burden which remained over time. 27 of the 32 patients achieved the protocol-specified criteria to be written in the efficacy analysis population according to the centrally assessed RECIST v1.1. the overall response rate was 18.5% in these 27 patients. Best overall responses were CR in one patient, PR in 4 and stable disease in 7 patients. The patient who experienced a CR had been already treated with 8 lines of metastatic disease treatment including anthracyclinr, taxane, and platinum based regimens. One of the 4 patients experienced a PR were previously treated once, another received 3 lines of therapy before, and the last 2 were treated 4 times in the metastatic setting. [12]

Before treatment all patients have experienced chemotherapy for adjuvant treatment. Results proved that pembrolizumab showed acceptable safety and tolerability.

However, in the second phase of cohort A of KEYNOTE-086 study, pembrolizumab did not seem to be very effective to metastatic TNBC. In the sampling frame of 170 previously treated PD-L1 patients the overall response rate is only 5.3 %[13] and only 5.7% in the PD-L1 positive populations[14]. In cohort B of KEYNOTE-086, the ORR achieved 21.4% in untreated PD-L1 positive tumors, and achieved a median duration of response of 10.4 months[14]. To summarize, KEYNOTE-086 indicated that pembrolizumab is useful to previously untreated patients, but if the patient had been treated before, the drug became less effective.

3.2. Atezolizumab and TNBC

Leisha A.Emens, Cristina Cruz and their fellow scientists conducted a research to investigate the safety and the clinical benefits of atezolizumab monotherapy against TNBC.

In the 116 valid samples, ranging from 29-82 years old with a median of 53 years old, 73 experienced an treatment-related adverse event(TRAE). In the 73 cases 58 were grade 1 to 2. pyrexia(19), fatigue (15) and nausea (13) occurred more frequently than others, while diarrhea (12), asthenia(11) and pruritus(11) were also observed. Grade 3 and 4 adverse events were also reported, including pruritic rash, lichen planus and adrenal efficiency (grade 3) ,pneumonitis(grade 4). two unluckily experienced a grade 5 TRAEs, with one pulmonary hypertension and 1 death not otherwise specified in a hospitalized patient. 3 failed to continue atezolizumab treatment due to a TRAE and 11 had a dose interruption. most of these events occurred in the first year of treatment.

The median duration of response was 21 months. Patients whose PD-L1 expression reaches at least 1% of tumor-infiltrating ICs exhibited increased overall response rates (ORRs) and prolonged OS compared to those with less than 1% of ICs. Furthermore, elevated levels of ICs (>10%) were independently linked to higher ORRs and longer OS. [15]

In conclusion the trial revealed that atezolizumab monotherapy provided durable clinical benefits and were well tolerated in metastatic TNBC patients. [15]

3.3. Avelumab and TNBC

In 168 metastatic breast cancer patients, including 58 TNBC patients, avelumab treatment were given for 2-50 weeks. All patients who had previously undergone a median of 3 prior therapies, were followed for 6-15 months. TRAEs of any level was observed on 115 patients.Grade 3 or more TRAEs were observed in 13.7% of patients, including 2 treatment-related deaths. The confirmed ORR was 5.2% in the TNBC cohort. Notably, a tendency toward a high ORR were observed in patients with PD-L1 positive in comparison to the PD-L1 negative tumor-associated immune cells in the TNBC subgroup. [16]

4. ICIs combined with other methods of treatment

4.1. ICIs and chemotherapy

4.1.1. Pembrolizumab and chemotherapy

60 patients participated in the KEYNOTE-173 experiment from 18 February 2016 and 28 February 2017. 18 patients (30%) experienced immune mediated AEs and infusion reactions, including 6 grade ≥ 3 cases. The pCR rate across all cohorts were 60 %. 12 months event-free and overall survival rates ranged from 80% to 100% across all cohorts. [17]

The combination of neoadjuvant chemotherapy with pembrolizumab revealed an acceptable toxicity and promisable antitumor activity.[17]

In another trial, Brie Chun, Joanna Pucilowska and their fellow scientists investigated the effect of pembrolizumab with paclitaxel or capecitabine. Scientists collected blood and tumor biopsies from metastatic TNBC patients, using the same processing methods, and was compared with blood samples from another cohort of patients who were treated for early-staged breast cancer. Flow cytometry and TCR were used to identify treatment-related immunological changes in peripheral blood and those T cells in the tumor.[18]

When paclitaxel and capecitabine were used in combination with pembrolizumab, they produce similar time dependent lymphodepletions in measured peripheral T cell subsets. Both produce same results in T cell clonality and richness. Pembrolizumab with paclitaxel or capecitabine increased the rate of T cell division in tumors, but this increase in speed do not always occur in blood. [18]

Peter A Fasching, Alexamder Hein and their fellow scientists investigated the effect of nab-paclitaxel and epirubicin/cyclophosphamide in combination with TNBC, aiming for pathological complete response (pCR) firstly followed with safety and quality of life. Pembrolizumab was given with chemotherapy in 3 weeks on 50 patients. After 25 patients the trial was improved to give a pembrolizumab monotherapy before chemotherapy. [19]

33 patients have a pCR. The most common adverse effects of any level were fatigue (58.5%), peripheral sensory neuropathy (54.7%) and neutropenia (52.8%). The rate of pCR in the 27 patients given a pembrolizumab dose before chemotherapy was 59.3% and 73.9% in the 23 patients before the improvement in the trial.[19]

The trial produced an encouraging pCR rate with pembrolizumab and np or ec, with acceptable side effects, producing a possible and reasonable alternative to platinum-containing chemotherapy. However data is still needed from randomised trials to support the combination to replace the traditional platinum/anthracycline/taxane based chemotherapy. [19]

Javier Cortes, Amin Haiderali and their fellow scientists wishes to estimate the effect of neoadjuvant pembrolizumab combined with chemotherapy followed by adjuvant pembrolizumab in comparison with other neoadjuvant methods for early staged TNBC. Researchers searched EMBASE, MEDLINE, Cochrane Central Register of Controlled Trials, conference abstracts and clinical trial registries for randomized controlled trials of the effects of neoadjuvant treatment for early staged TNBC. To estimate the effect of relative treatment on evaluated interventions, NMA was performed.[20]

Between June 2016 and May 2017, 17 out of 19 patients who were accessed for eligibility were enrolled. 11 patients experienced a grade 3 adverse event of any cause, such as dyspnea (3) fatigue (2) and infection (2). A grade 4 lymphopenia was observed. 9(53%) patients in total have experienced an adverse event at least once, such as radiation dermatitis (29%), fatigue (18%) skin changes and nausea (12%), including 3 grade 3 and 1 grade 4 events. No patients stopped the therapy for AEs and no deaths was caused by the study. [20]

In this trial the new combination of treatment were better in response and survival outcomes compared with the alternative neoadjuvant treatment in early-stage TNBC. [20]

4.1.2. Nivolumab and chemotherapy

The trial aimed to investigate the immunologic effects of nivolumab, capecitabine or the combination of both by evaluating the PIS (primary endpoint).

45 women with TNBC and residual invasive disease after standard neoadjuvant chemotherapy were given nivolumab, capecitabine or both in combination randomly. Result showed that a the combination of nivolumab and capecitabine is more effective in increasing PIS(91%) from the first day to week 6 than nivolumab(47%) or capecitabine (53%) monotherapy, showing its effectiveness.[21]

4.1.3. Atezolizumab and chemotherapy

Foluso O Ademuyiwa, Feng Gao and fellow scientists evaluated the effect of neoadjuvant carboplatin and paclitaxel in combination with atezolizumab compared with chemotherapy alone in stages II to III TNBC. To measure the effect researchers must evaluate if the combination increased pCR rate and TIL percentage compared with chemotherapy alone in the mITT population.[22]

67 patients (25-78 years; median 52 year) were randomly separated so that 22 belongs to arm A and 45 to arm B. in all the patients who were given at least 1 dose of combination therapy, arm A had a pCR rate of 18.8% and arm B had a pCR rate of 55.6%. a ≥ 3 TRAE appeared in 62.5% of patients in arm A and 57.8 % in arm B. A patient died due to a recurrent disease in the follow-up period in arm B. Although the presence of a small sample size have lead to a limited subgroup analyses, PD-L1 positive patients given atezolizumab and chemotherapy still achieved a pCR rate of 75% (12/16).

The combination of atezolizumab and neoadjuvant carboplatin or paclitaxel have lead to an enormous increase in pCR rate in patients with stage II and III TNBC.[22]

Bin Wu and Ma Fei investigated the cost-effectiveness of atezolizumab and nab-paclitaxel on advanced TNBC from the US patients' perspective by adopting a Markov model and measuring the incremental cost-effectiveness ratio (ICER).[23]

Results showed that the combination therapy cost $ 104,278 compared to $149,465, and an ICER of $281448 and $196073 per QALY gained. The combination therapy maintains a trend of increasing net health benefits. The probability of cost-effectiveness at the level of $200,000/QALY is more than half of subgroups with PD-L1 positive is greater than 50%. [23]

To summarize, the combination therapy is likely to be a cost-effective option in comparison with nab-**paclitaxel chemotherapy in advanced TNBC.[23]**

4.2. ICI and radiotherapy

Alice Y Ho, Christopher A Barker and their fellow scientists investigated the effect of radiotherapy with pembrolizumab in metastatic TNBC patients unselected for PD-L1 expression.[24]

17 patients were enrolled in total, with median age 52 years old (Range, 37-73 years). a radiotherapy dose of 3000 centigrays were given 5 times a day. 200 mg of pembrolizumab was injected through vein within 3 days after the radiotherapy dose, then given every 3 weeks±3 days until disease progression. The median follow-up was 34.5 weeks.[24]

The overall response rate of the 17 participants was 17.6% with 3 complete responses, 1 stable disease and 13 progressive diseases. 9 women were evaluated the RECIST version 1.1 at week 13, in which 3 achieved a complete response and all had a reduction of tumor volume outside the irradiated portal. Dermatitis appeared to be the most common(29%) grade 1-2 toxicity. The use of pembrolizumab have lead to fatigue, lymphopenia and infection, all being grade 3 AEs. No grade 4 or above AEs were reported.[24]

The combination therapy were proved as safe and have shown encouraging activity in metastatic TNBC patients. However, more clinical trials of these combination therapy were needed.

5. Conclusion

In this study, we will examine the impact of ICI monotherapy, ICI in combination with chemotherapy, and ICI combined with radiotherapy on the treatment outcomes. The findings indicate that ICI monotherapy, the combination of ICIs with chemotherapy, and the combination of ICI with radiotherapy have significantly enhanced overall response rate (ORR), progression-free survival (PFS), and overall survival (OS) in comparison to conventional chemotherapy. Moreover, the combined therapies have demonstrated greater cost-effectiveness when compared to ICI monotherapy.

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