Use of Immunotherapy in Triple Negative Breast Cancer

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Introduction

Cancer is a disease characterized by the uncontrollable growth and spread of abnormal cells. The symptoms of cancer can vary based on the locations and stage of the disease. The immune system is a network of organs and cells used as a defense mechanism to protect the body from infections and diseases, such as cancer itself. The immune system should be able to recognize cancer cells and immediately eliminate them. However, cancer cells use different strategies to avoid attacks from the immune system. These strategies are known as evasion mechanisms. Immunotherapy is a type of treatment that uses medicine to either activate or suppress the immune system in order to fight cancer cells, and defeat the disease. Since this type of therapy targets cancer cells more easily, it tends to be a more attractive option. Currently, a lot of the treatments used are antigen specific, however, immunotherapy alters the approach, enabling and strengthening the whole immune system. In this review, we will describe the use of immunotherapy in Triple Negative Breast Cancer (TNBC).

Triple Negative Breast Cancer (TNBC) is one of the most aggressive types of breast cancer, known for its absence of estrogen receptor (ER) and progesterone receptors (PR), and the human epidermal growth factor receptor 2 protein (HER2). The disease often targets women who are carriers of the Breast Cancer Gene 1 mutation (BRCA1). This is a gene that produces proteins which help repair damaged DNA and prevent cells from growing out of control. When mutated, the gene is unable to suppress tumors, causing the mutation to increase the risk of cancer. TNBC is often found in many young women who are carriers of BRCA1. The incidence of the BRCA 1 mutation within the general population is 1 in every 300 to 800 people (Casaubon et al., 2023). Luo et al. (2022) found that those who had a survival rate longer than the five year mark were younger than fifty-five years of age and Caucasian.

Conventional therapies such as radiation, chemotherapy and hormonal therapies target cancer through their focus on the hormonal receptors and shrinking tumors. However, due to the absence of hormonal receptors in TNBC, these conventional therapies are ineffective. Immunotherapy offers a different approach. Immune checkpoint inhibitors (ICI) are regulatory proteins on immune cells that help maintain balance on immune responders (Berger et al., 2021). These inhibitors allow the T cells to stay active and attack cancer cells. For instance, cancer cells use a protein called PD-L1 (Programmed death-ligand 1) to evade the immune system by using protein to camouflage themselves. However, the Immune Checkpoint inhibitors (ICI), specifically Keytruda (Pembrolizumab) block this mechanism, by activating the immune system.

Additionally, recent research highlights the role of UBR5, a ubiquitin protein ligase, that helps the cancer cells evade immune surveillance by safeguarding PD-L1. UBR5 prevents the PD-L1 from being degraded by ensuring that the protein remains on the surface of the cancer cells. The recent research in understanding the role of UBR5 contributes to the new development of treatments that target UBR5. If these treatments can reduce and stop UBR5

from working, there will be less protection of cancer cells as their defense mechanisms will weaken. Furthermore, T cells and other immune cells such as dendritic cells are often dysregulated, which means their function is abnormal, further allowing the tumor to evade the immune system (Wu et al., 2022). The Food and Drug Administration (FDA) has approved therapies such as Paclitaxel, docetaxel, doxorubicin, epirubicin and Keytruda (Mandapati & Lukong, 2022).

One current trial is a Phase II randomized open-label trial. Phase II is the stage which evaluates how well the combination treatment works in a group of patients with TNBC (NCT04373031). This study looks into pembrolizumab, a type of immunotherapy that targets the PD-1/PD-L1 pathway, activating the immune system to attack cancer cells, along with chemotherapy as a treatment given before surgery for TNBC. The trial assesses different ways of applying the immunotherapy treatment to see how it affects both the cancer and the immune system. The typical used neoadjuvant regimen for TNBC often includes weekly taxane for 12 weeks, followed by an anthracycline every 3 weeks for 4 cycles. This study combines the neoadjuvant regimen, the chemotherapy regimen, followed by Pembrolizumab in a randomized multi-arm trial that assigns patients to the two different protocols. In addition, their TNBC must be confirmed as locally advanced, non metastatic (M0), and defined as specific T (primary tumor) and N (regional lymph node) based on the most recent ASCO/CAP guidelines and AJCC Version 8. Patients need to provide a core needle biopsy of the primary tumor, and have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 assessed within 14 days of treatment initiation. Exclusion criteria include prior malignancy within the past 5 years, recent therapy including chemotherapy, targeted therapy, or radiation therapy within the past 12 months, prior immunotherapy, prior participation in recent clinical trials within 4 weeks of the first dose of treatment, received a live vaccine within 30 days, and diagnosed autoimmune conditions. Additionally, exclusion criteria include current immunodeficiency or immunosuppressive therapy 7 days prior to treatment.

Another ongoing combination therapy trial (NCT05491226), studied by Stephen Shiao, examines the TNBC response to immunotherapy with combination Myeloid Inhibition and Radiation. This study is a Phase II trial where pembrolizumab is combined with radiation therapy and CSF-1R inhibition for patients with high-risk TNBC. The main goal is to determine how often patients become cancer-free in the breast and lymph nodes after standard treatment. Secondary goals include examining the change in immune cells within tumors, studying the safety of the treatment mix, and monitoring survival and disease progression. In order to be eligible, patients must be females, age 18 or older with a diagnosis of high-risk triple negative breast cancer (TNBC). In addition, patients must have a low tumor-infiltrating lymphocyte (TIL) score, have available archived tumor tissue for analysis, ECOG performance status of 0 or 1, adequate organ function, a negative serum or urine pregnancy test within 14 days of starting pembrolizumab, and comply with contraceptive guidance during the treatment period. Exclusion criteria include evidence of metastatic disease, recent radiotherapy, recent participation of other trials within 4 weeks, immunodeficiency or immunosuppressive therapy within 7 days, tuberculosis, hypersensitivity to pembrolizumab, recent monoclonal antibody therapy, recent chemotherapy or targeted therapy, additional malignancies within the last 5 years, autoimmune diseases, lung diseases, and active infections. Ongoing clinical trials address earlier limitations through combination treatments of immunotherapy and either chemotherapy or radiation

therapy. A combined therapy targets both mechanisms of treatment. For example, in this specific study, the combination of radiation and immunotherapy improves the effectiveness of the immunotherapy. When combined, radiation enhances the visibility of cancer cells to the immune system, allowing the immune system to better target and fight the cancer cells. Clinical trials exploring the combination of therapies are designed to investigate safety and tolerability, efficacy, and the optimal sequencing to maximize benefits and minimize risks.Ultimately, the exploration of combination therapies, specifically the mix of immunotherapy, chemotherapy, and radiation therapy broadens treatment options and improves the outcome.

Conclusion:

This article reviews Triple Negative Breast Cancer (TNBC), a type of breast cancer that lacks the common receptors estrogen, progesterone, and HER2. Immunotherapy is the emerging new treatment for TNBC and clinical trials have shown meaningful tumor responses and successful remissons. However, it remains challenging due to TNBC's aggressive nature and limitations as responses vary across patients. Combination therapies provide a more comprehensive approach, enabling more customized approaches for a patient, maximizing benefits and effectiveness. Researchers are currently focused on further understanding the mechanism by which these immunotherapies work, sequencing of combination therapies, overcoming resistance and managing side effects. Looking towards the future, the goal for immunotherapy is to be able to successfully treat TNBC with long term benefits, saving many people's lives.

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