The use of immunotherapy to treat Triple Negative Breast Cancer

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Cancer is characterized to be an uncontrollable growth of cells, leading to tumor formation that can occur anywhere and spread throughout an individual's body. The immune system is a network of different organs, tissues, and white blood cells which help the body fight off diseases. The immune system has two main parts which help defend: the innate system, and the adaptive system which help fight off pathogens. The innate system responds quickly to diseases but has no future immunological memory, meanwhile the adaptive system has a delayed defensive response but holds immunological memory to prevent future attacks from the disease (Delves 2020). Cancer generally avoids the immune system by downgrading MHCI so the T cells cannot recognize the cancer as a threat, as well as blocks costimulation, so T cells cannot be fully activated and upregulate immune checkpoints to turn T cells response off. Immunotherapy is a form of cancer treatment that enables the immune system in fighting off cancer and other various diseases. Immunotherapy is attractive to individuals since it utilizes the immune system to induce an anti tumor response to defeat cancer (Zhang 2018). In this review we discuss how antibodies and combination therapies can be used to treat Triple Negative Breast Cancer, and how upcoming advancement of these techniques can potentially increase future survival rates for patients.

Triple negative breast cancer (TNBC) is aggressive, has a rapid growth rate,and lacks treatment options, motivating the need for multifaceted solutions. TNBC is an aggressive form of cancer which lacks common receptors found in common breast cancers, breasts possess common receptors such as estrogen, progesterone and HER2 proteins throughout them, though breast cancer such as TNBC affects the amount of these receptors causing changes which alter how the cells grow. TNBC cannot be associated with a certain cause although researchers know it descends from a family history of breast cancer, or gene mutations such as the *BRCA* genes. This disease primarily impacts premenopausal women and those under 50. The American Cancer society notes that African-American women have a more advanced stage distribution for breast cancer compared with caucasian American women and higher incidence rates for TNBC, as well as the Caribbean suffer from TNBC since it varies between 11% and 38.5% of all breast cancer cases which were diagnosed throughout the region, (Tiscoski 2023). Many Latin American women are affected by TNBC more than a caucasian people as well. Triple negative breast cancer carries highly recurrent mutation genes, such as *TP53*, which provides instructions to make tumor protein, and this protein acts as a tumor suppressor gene. Another mutation includes *PIK3CA*, which provides instructions for p110 alpha an enzyme; if it is mutated it causes overactive enzymes causing cancer cells to grow and spread. Individuals with various stages of cancer have differing survival rates; individuals had a 90% survival rate recorded after 5 years, the regional stage more than 60% survivors after 5 years, and in the distant stage only around 10% of people survived, (Hsu 2022). TNBC has a 5 year relative survival rate of 81.28%. If the TNBC is metastasized the survival rate for an individual will reduce to around 13 months, but with treatment this can improve (Chue 2019). Often many individuals who have TNBC first need to have a lumpectomy to remove the lump, or mastectomy to have their whole breast removed. Afterwards chemotherapy or radiation is used

to target the cells left over from surgery. Chemotherapy also reduces the chance the cancer can grow back, although TNBC is known to be the most aggressive type of cancer which also reduces the survival rate and the chance it will grow back is higher. TNBC's aggressive form causes the tumor to grow 1% each day, causing it to be one of the fastest growing cancers, (Lee SH 2016).

Breast cancer's vitality depends on the cell's ability to spread and live in an individual's system. TNBC presents tumor specific antigens. The breast cancer cells increase Mal, a T Cell Differentiation Protein 2. (MAL2) is a protein encoded by the MAL2 Gene, used for transcytosis which carries proteins to the surface. Breast Cancer often dysregulates Gab1 which is a protein integrator of cell signaling pathways and regulating cell survival, so in order for successful treatments and interventions to form, researchers need a clear understanding on what happens during BC and how they can prevent it. TNBC has various immunotherapy options including Pembrolizumab, a form of antibody which binds to PD-1 protein on the surface of T cells, then prevents PD-1 from binding to PD-L1, and PD-L2 ligands that would be deactivated and prevents an immune response, which keeps cancer cells from suppressing the immune system, (Dong 2017). Another immunotherapy is Trodelvy which is an antibody target to help get rid of cancer, it interferes with a cell's ability to replicate. Just like Nivolumab which is a form of (ICI) Immune checkpoint inhibitor a drug that blocks and alters checkpoints, Nivolumab is a monoclonal antibody which binds to PD-1 T cells and keeps cancer from suppressing the immune system. Additionally it targets anti-PD-1 receptors and prevents obstruction of the activation signal for T cells. Combining chemotherapy and ICI results in a higher percentage of elimination and preventing the cancer from regrowing in an individual's system. Trodelvy immunotherapy targets TROP-2 cells, a form of glycoprotein antigen 2. It is a signal transducer and signals cells for self-renewal and survival, and Trodelvy works by delivering strong chemotherapy into TROP-2 cells. The overall effectiveness of Pembrolizumab immunotherapy against TNBC is 18.5% because some cancer tumors have decreased MHC, a major histocompatibility complex which is a group of genes which code for finding unfamiliar substances, they have MHC molecules which bind fragments from pathogens and display them on a cells surface for recognition by T cells, overall involved in antigen presentation for the T cells (Janeway 2001). Trodelvy's effectiveness rate sits at 4% for a complete response and 31% for partial response. Additionally, Nivolumab's success rate sits at 25.1%. The success rate is defined by various measured endpoints in trials, such as its overall survival rate, progression free survival, disease free survival, response rate, and the 5 year survival. Overall immunotherapy use in the TNBC setting helps strengthen and restore the immune system's ability to fight against cancer cells, and the upcoming evolution of immunotherapies has a beneficial uprising, seen already through the uprise in research and new forms of therapies to treat TNBC. TNBC limitations are caused by the various molecular subtypes which impact current and upcoming treatments and the resistance some patients' cancer cells build to antigens. The FDA had approved Atezolizumab with a combination paclitaxel which became the first FDA approved treatment for metastatic TNBC, (Soare 2019). The FDA also recently approved a combination of pembrolizumab and chemotherapy. Atezolizumab, an ICI, is a monoclonal antibody used to treat various types of cancer; it binds to PD-L1 on cancer cells which keep the cancer from getting to the immune system. Though recently it was withdrawn from FDA approval list due to treatment with Atezolizumab not meeting standard for progression free survival in adults whose tumors had PD-L1. Atezolizumab failed to meet the primary

endpoints in the treatment of patients' overall survival. Including how 18% of individuals whose main antibody was this specific drug had adverse reactions. Pembrolizumab came into the scientific world which changed the TNBC treatment landscape, and atezolizumab no longer would surpass or meet the standards of new and improved treatments (Jacobs 2023).

An ongoing phase 3 trial ASCENT-05 comares the effectiveness and safety of trodelvy in combination with pembrolizumab before and after surgery in early diagnosed stage patients (NCT05633654). This trial is also testing to see if the combination of pembrolizumab with another drug offers better disease free survival than just pembrolizumab alone. The trial is enrolling people diagnosed with stage I, stage II, and stage III (early-stage) triple-negative breast cancer with residual disease. As of right now 1514 patients are enrolled in the trial and the trial is being only done on adults. Individuals are eligible if they have been diagnosed with early stage non metastatic TNBC and have residual disease (small amounts of cancer cells still remain in the body) after surgery or chemotherapy . Individuals are also eligible if they have received appropriate radiation therapy and have recovered from the side effects, and their Eastern Cooperative Oncology Group (ECOG) performance status 0-1, which indicates an individual is fully active or restricted in strenuous activity. Individuals are not eligible if they have been diagnosed with stage 4 metastatic breast cancer or previous primary breast cancer. They are not eligible if they have a *BRCA* mutation, had any anti-HER2 medicine, received other types of immunotherapy, or have been diagnosed with recurrent breast cancer after therapy. Another criteria is a patient is not eligible if they have received a treatment containing a topoisomerase inhibitor, which is a sort of inhibitor that blocks the ligation step of the cell cycle leading the cells to apoptosis. The current treatment being tested is the combination of Anti-TROP2 antibody-drug conjugate sacituzumab govitecan (trodelvy) + pembrolizumab and pembrolizumab +/- capecitabine. Capecitabine is a type of chemotherapy which stops cells from repairing and making DNA. This trial with the combination of (SG), Sacituzumab govitecan-hziy known as Trodlevy plus pembro has the potential to improve clinical outcomes in patients with TNBC. This trial can address the limitations of successful treatments against recurrence and metastasis in TNBC; when successful it can challenge those limitations by being a reliable successful option. The future goal for this trial is to possibly see if the trial is effective and safe compared to the treatment of physician's choice (TPC). A second phase 2 trial is OCTANE which aims to evaluate various measures of liposomal, doxorubicin, and carboplatin combination therapy in early stage TNBC patients (NCT05949021). Liposomal doxorubicin is a chemotherapy drug that blocks the enzyme (topoisomerase 2) which cancer cells need in order to grow and divide. This trial also focuses on evaluating changes in circulating tumor DNA and seeing if it has a potential to become a biomarker for treatment response and progression in the future. The trial is currently in phase 2 where doctors gather preliminary data on whether the combination works on people with early stage TNBC. Currently this trial has around 20 people but many researching programs in various hospitals are still recruiting for many individuals. This trial is also gender based and only looking for female individuals, adult, child, and older adult. To be considered eligible the patient must be recently diagnosed with early stage BC, have completed prior surgical treatment, ECOG performance 0-1, adequate bone marrow and hepatic function, and willingness to comply with the trial's rules. Exclusion criteria from this trial includes participants with stage 3-4 TNBC, uncontrolled hypertension, active liver disease,pre-existing neuropathy greater than 1, clinically significant cardiac disease, uncontrolled infections, and non-healing wounds. Current treatments being tested are the combination of liposomal

doxorubicin with carboplatin therapy. Carboplatin therapy is a type of chemotherapy which slows or stops the growth of cancer; the risk is it can decrease the amount of blood cells in bone marrow which requires any eligible participants to have healthy bone marrow. This trial can also address the earlier limitations of successful treatments for recurrent TNBC; if successful this can be a great option for many females throughout the world to use. Future directions for this trial aims to contribute to the understanding of the benefits and risks associated with liposomal doxorubicin and carboplatin combination therapy in early stage TNBC, which might lead to improvement in treatment outcomes and patient care. Since both studies are still around phases 2-3 the treatments and are relatively new, complete conclusive results are yet to be obtained.

Triple negative Breast Cancer is a form of aggressive cancer which lacks certain receptors deriving from a mutation inside of the *BRCA* gene. Although Monoclonal antibodies, chemotherapies and immunotherapies are used for treating TNBC, their effectiveness varies due to TNBC being the most difficult cancer to treat. The main challenges researchers encounter while treating TNBC is finding treatments which specifically target estrogen receptors, progesterone receptors and human epidermal growth factor receptors, which don't respond to specific targeted drugs (Obidiro 2023). Immunotherapy used to treat TNBC includes monoclonal antibodies, chemotherapies, and combinations, and so far have been successful in reducing and treating TNBC. Currently researchers are working on advancing treatments for TNBC by developing various forms of therapies such as combination therapies, while trying to use upcoming and successful FDA approved medication. With new advancements and continued clinical research, immunotherapy for TNBC has the potential to enhance efficiency of targeted treatments and expand the overall survival rate of patients diagnosed with TNBC, forever changing the landscape of TNBC treatment.

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