Analyzing the role of the immune system and Immunotherapy in Triple Negative Breast Cancer (TNBC) Management

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Abstract. Triple negative breast cancer TNBC is the type of breast cancer that does not have Estrogen receptor, Progesterone receptor and human epidermal growth factor receptors 2 (HER2) when stained with the Immunohistochemistry stains. As it's lacking the targets for most chemotherapy medications, it has a more aggressive course, a poor prognosis, higher chances of relapse and usually diagnosed at a later stage. In this review, we are illustrating how the immune system can be manipulated to attack the micro-environment that the cancer creates to escape and thrive. Also, we are discussing the signaling pathways of the immune system on which the immunotherapy medications were based and the different chemotherapy options that are used in the same regiment for management of TNBC.

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Keywords: Triple negative breast cancer; TNBC; PD-1/PD-L1; CTLA-4; TILs; avelumab; atezolizumab; pembrolizumab; Tremelimumab; Ipilimumab; TMB.

1. Introduction and background:

Breast cancer is considered the second leading cause of death worldwide, after lung cancer. Based on Immunohistochemistry stains of Estrogen receptor, Progesterone receptor and human epidermal growth factor receptors 2)HER2(, the cancer is classified in to different types. Triple Negative Breast cancer is the type of breast cancer that lacks expression the three receptors: ER, PR and HER2, which makes it lacking the target of most chemotherapy that is used for treatment of breast cancer. TNBC represents 10-20% of all diagnosed breast cancers. It is more prevalent in younger ages and in African-American females. It has a more aggressive course, a poor prognosis, higher chances of relapse and usually diagnosed at a later stage compared to the other types (Mehanna et al., 2019; Keihan Shokooh et al., 2021). On the other hand, it has a higher percentage of BRCA mutation than other types, that reaches up to 35% of BRCA1 mutation. BRCA1 is a well-established tumor suppressor gene re-sponsible for DNA stability and DNA double-strand break repair through homology-directed repair and non-homologous end joining (Yoshida, K., & Miki, 2004; Roy et al., 2012; Zhang, J., & Powell, 2005).

Triple negative breast cancer usually appears as an invasive ductal carcinoma. Based on the gene expressing profiles, there are six distinct types of TNBC have been identified: basal-like 1 and 2 (BL1 and BL2), mesen-chymal, mesenchymal stem-like, immunomodulatory and luminal androgen receptors (LAR). Each type of these seven have a different clinical behavior and tends to respond very well to a certain medication (Lehmann et al., 2011).

Basal like 1 and 2 are the most common. They are the type that is most associated with BRCA mutation. BL1 has high expression of genes in-volved in cell-cycle regulation, cell proliferation, and DNA damage response, while BL2 has high expression of genes involved in cell division, cell division, and growth factor signaling. BL1 achieve higher higher pathological complete response (pCR) rate when given neoadjuvant chemo-therapy. Where as BL2 subtype tumors has higher risk of recurrence. Both respond well to anti-mitotic taxanes (paclitaxel or docetaxel) and PARP inhibition (Vagia et al., 2020).

Mesenchymal and mesenchy-mal stem-like express a higher number of genes involved in growth factor signaling (EGFR, PDGFR, PI3K/mTOR, Src) and responded well to PI3K–mTOR inhibition (Pareja, & Reis-Filho, 2018). The immuno-modulatory subtype (IM) expresses NFKB, TNF, JAK, and cytokine signaling genes, which are involved in antigen presentation and immune processing. The hig expression of immune-regulators CTLA4, PD1, and PD-L1 in TNBC caused by lymphocyte infiltration is likely linked to immune checkpoint inhibitor response. LAR are identified as such because of their apocrine histological differentiation that is similar to luminal hormone receptor positive tumors with this name.

LAR tumors are of lower grade, involves more lymph nodes, occur in older women, and have low pCR rate when treated with neoadjuvant chemotherapy. Most of the lobular TNBC are of the LAR type. They express genes involved in steroid hormone synthesis and androgen metabolism.

With the TNBC lacking the major receptors being targeted in most chemotherapy medica-tions, it makes treating this type of cancer a hard battle to win and may lead to disease progres-sion and metastasis. Breast cancer spreads to surrounding lymph nodes and farther through the body to areas such as the bones, lungs, liver, and brain in most stage IV cases. An estimated 1 million cases of breast cancer are diagnosed per year around the world, with over 170,000 cases identified as triple-negative breast cancer (TNBC) (Marra et. al., 2019). In this article, we will review the ad-vances in the treatment of each subtype focusing on the immunotherapy till this present moment and the future considerations of possible modes of treatment.

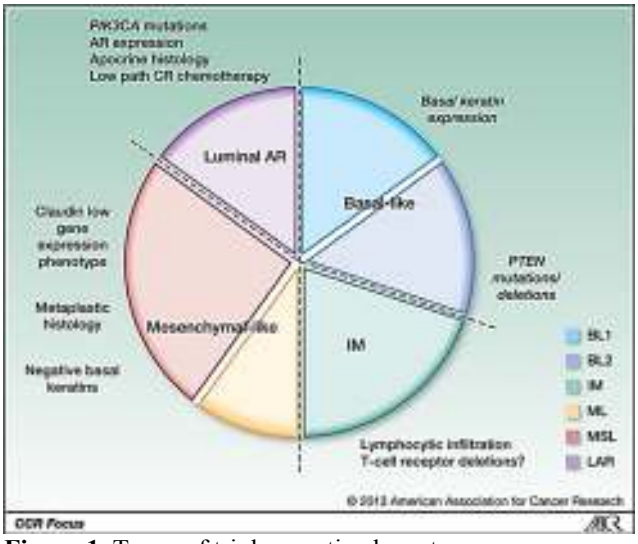

Figure 1. Types of triple negative breast cancer.
(AR, FOXA1, GATA3) and responds to anti-androgen therapy (Vagia et al., 2020).
https://clincancerres.aacrjournals.org/content/19/23/6380

2. Discussions:

2.1. The interaction between the immune system and the tumor

In the recent studies over the past few years, there has been a great advancement in the treatment of TNBC based on role of the immune system to fight the cancer. In 2018, the Nobel Prize in Physiology or Medicine was awarded by the Nobel Assembly at Karolinska Institute to James P. Allison and Tasuku Honjo for their research in inhibiting the negative immune response to fight cancer. They demonstrated certain immune check points like the programmed cell death protein 1 (PD-1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) can act as a brakes for the immune system to reactivate T cells to fight the cancer cells (Bader et al., 2017). To maintain self-tolerance and reduce bystander tissue damage as a result of immune response vs. pathogenic invasion, in-hibitory receptors, also known as immune checkpoints, control CTL activation and effector functions.

2.2. Prognostic Immunologic biomarkers in TNBC and the correlated immunotherapy medications

It has been discovered that certain immunological biomarkers have a big impact on the treatment process and predicted the prognosis of the diseases. Some of there biomarkers include: Tumor-infiltrating lymphocytes (TILs), Programmed death-ligand 1 (PD-L1) expression, Cytotoxic T lymphocyte associated antigen 4 (CTLA-4), Gene signatures, Tumor mutational burden (TMB) and microsatellite instability (MSI), and mismatch repair (MMR) deficiency (Marra et. al., 2019).

Programed death protein ligand 1 (PD-L1) expression was detected in the cytoplasm and cell membrane of tumor-infiltrating lymphocytes (TILs) in breast cancer tissue samples, but not in healthy human lymphocytes, as diffuse brownish yellow granules. Positive expression of PD-L1 was observed in 47% of patients with invasive breast carcinoma, compared to 69.3% of TNBC patients ($P<0.05$) (Meng et al., 2020).

2.2.1. Tumor-infiltrating lymphocytes (TILs)

TNBC is on of the types of cancers that is characterized by a heavy load of lymphocytes in the tumor tissues, that are called Tumor-infiltrating lymphocytes (TILs). The stromal TILs in between carcinoma cells are characterized as mononuclear host immune cells (mostly lymphocytes) that are present within the tumor's boundary but do not directly touch or infiltrate tumor cell nests. Stromal TILs (sTILs) are expressed as a percentage of the total stromal region in the tumor occupied by lymphocytes (i.e., not the percentage of cells in the stroma that are lymphocytes). While Intratumoral TILs (iTILs) are lymphocytes found inside carcinoma nests that have direct cell-to-cell contact with no intervening stroma. Both types of TILs have a prognostic value in patient with TNBC (Kos et al., 2020).

Clinical outcome is determined not only by the sum of lymphocytic infiltration, but also by the phenotype of that infiltrate. Type 1 T-cells are linked to a better prognosis. Antigen presentation is aided by CD4+ T-helper 1 (Th1) cells secreting cytokines and activating antigen-presenting cells. Also, CD8+ cytotoxic T-cells (CTL) plays an important role in tumor cells destruction. Meanwhile, Type 2 CD4+ T-helper cells (Th2), such as Forkhead box P3 (FOXP3) CD4+ regulatory T-cells inhibit CTL activity, support B-lymphocyte proliferation, and may promote an anti-inflammatory immune response that may promote tumor development (Stanton, & Disis, 2016).

TNBC is on of the cancers in which the percentage of the TILs present in tumor tissue plays a pivotal role in the prognosis, success of treatment and the overall survival of patients. As TILs and PD-L1 presented on their surface being a direct target for immunotherapy, several studies has shown that there is a direct correlation with the TILs load in the cancer and the prognosis. With each 10% decrease the fraction of TILs, there is a 20% increase in the risk of mortality in TNBC patients (Vihervuori et al., 2019).

series and is a 33-kDa type 1 transmembrane glycoprotein that contains 290 amino acids with Ig- and IgC domains in its extracellular region. PD-L1 is expressed by macrophages, activated T cells and B cells, DCs and some epithelial cells (Vihervuori et al., 2019). PD-L1 expression has been shown to be elevated in melanoma, lung, bladder, colon, liver, and head-neck cancers. Alt-hough several meta-analyses have shown that its over-expression predicts a poor prognosis in a variety of cancers, the expression of PD-L1 in breast cancer is poorly understood, and its prognostic importance is uncertain (Lotfinejad et al., 2020).

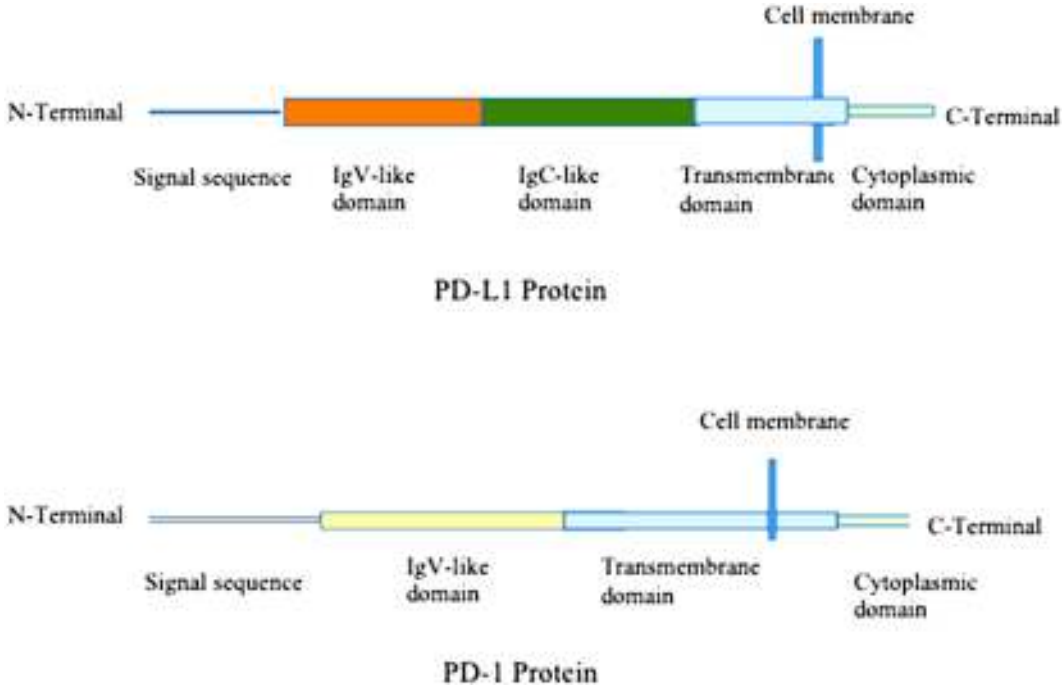

Figure 2. PD-1 and PD-L1 structure
https://jhoonline.biomedcentral.com/articles/10.1186/s13045-019-0779-5/figures/1

2.2.2. Programmed death protein /Programmed death-ligand 1 axis (PD-1/PD-L1)

The programmed cell death receptor 1 / programmed death-ligand 1 (PD-1/PD-L1) axis is a means by which the tumor cells escape the immune response that is directed towards the tumor cells. The programmed cell death receptor 1 is present on the surface of the TILs (Meng et al., 2020).

PD-1 or CD279 is a 55-kDa transmembrane protein formed of 288 amino acids with an extra-cellular N-terminal domain (IgV-Like), a membrane-permeating domain at the at the N end and a cytoplasmic tail located at the C end with two tyrosine base. PD-1 is expressed on activated T, natural killer (NK) and B lymphocytes, macrophages, dendritic cells (DCs) and monocytes. PD-1 inhibits both adaptive and innate immune responses (Han et al., 2020).

PD-1 ligand or B7-H1 that is encoded by the CD274 gene localized on chromosome 9p24.1, belongs to the B7

The expression of PD-L1 was found to be significantly asso-ciated with WHO grade, nerve invasion, Ki67, CK5/6, and EGFR in TNBC patients ($P<0.05$). These findings indicate that PD-L1 expression is linked to the majority of pathological features in patients with invasive breast cancer, possibly reflecting tumor burden (Meng et al., 2020). Costa et al. found that 45% of TNBC patients had positive PD-L1 expression in their study (Costa et al., 2018). It has been shown in Baptista et al that 50% of the breast cancer patients with PD-L1 expression showed longer over-all survival OS, not considering the TNBC subtype. Saboteur et al found that basal breast cancer patient who express PD-L1 showed longer metastasis-free interval. Beckers et al observed that patients with tumor PDL1 expression had a lower breast cancer specific death rate, and that patients with stromal PD-L1 expression had a lower all-cause death rate (Mirili et al., 2020).

PD-L2 shares 60% amino acids with the PD-L1 and considered as the second ligand for the PD-1 protein.

Unlike PD-L1, it's expression is limited to activated dendritic cells, macrophages, bone marrow derived mast cells and peritoneal B1 cells. PD-L2 is usually expressed with the PD-L1 but by a lesser extent. It's main function is not yet clear, that's why we will discuss mainly the PD-L1/PD-1 axis (Seliger, 2019).

The PD-1/PD-L1 pathway, under normal non cancerous circumstances, regulates the degree of inflammation at locations expressing antigens to protect the normal tissue from excessive tissue injury.

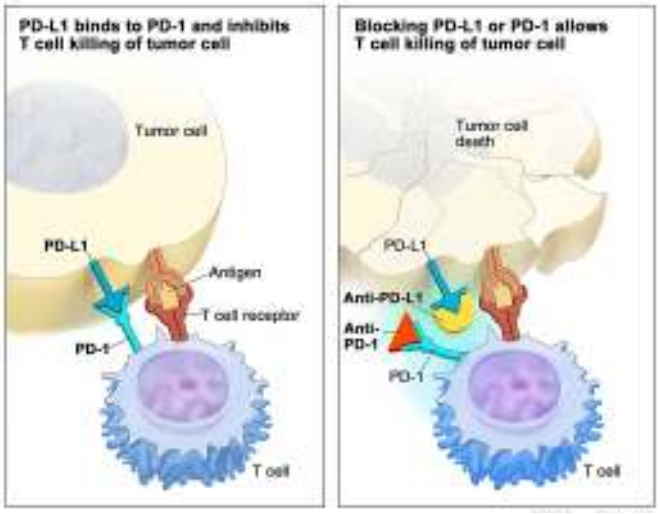

Figure 3. Normal PD-1/PD-L1 interaction and blocked PD-1/PD-L1 interaction
https://www.cancer.gov/publications/dictionaries/cancer-terms/def/immune-checkpoint-inhibitor

Inflammatory cytokines are released when a T cell recognizes the antigen expressed by the MHC complex on the target cell, which starts the inflammatory process. These cytokines trigger tissue PD-L1 expression, which activates the PD-1 protein on T cells, resulting in immune tolerance, a state in which the immune system loses control of mounting an inflammatory response even though actionable antigens are present (Mahoney et al., 2015).

Tumor microenvironment is a state in which the tumor changes in its surroundings to enhance its progression by recruiting stromal cells to provide growth signals favoring cell proliferation and metastasis. The tumor cells escape the immune response by over expression of the PD-L1 on their surface. Thus the interaction between the PD-1/PD-L1 allows the tumor cells to grow and proliferate. PD-1 and its ligand PD-L1 play a significant role in tumor growth and survival in the tumor microenvironment by evading tumor-neutralizing immune surveillance.

The interaction between the PD-1 presented on the Cytotoxic T lymphocytes and PD-L1 on the tumor tissues allows the tumor cells to evade the immune system by causing T cell dysfunction, exhaustion, apoptosis, neutralization, and interleukin-10 (IL-10) production and inhibit stimulatory cytokines production in a tumor mass. Tumor cells become very strong and secrete many pro-inflammatory cytokines, such as tumor necrosis factor alpha (TNF-α), interleukin-2 (IL-2), and interferon gamma (IFN-γ), as a result of CD8+ T cell exhaustion (Colafrancesco et al., 2017). This gives the basis for using the PD-L1 inhibitors, by blocking the PD-1/PD-L1 interaction, you allow the immune system to recognize the tumor cells and fight it. Though there is one limitation that this medication has faced was the number of the T cells already present in the tumor tissue (Colafrancesco et al., 2017).

Examples of the humanized monoclonal antibody medications that target the programmed death protein /Programmed death-ligand 1 axis (PD-1/PD-L1) pathway are **avelumab** and **atezolizumab** against PD-L1 and **pembrolizumab** against PD-1.

2.2.3. The cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4)

Another prognostic factor that was discovered in the studies in the previous years was the Cyto-toxic T lymphocyte associated antigen 4 (CTLA-4), as CTLA-4 is associated with a poor progno-sis in breast cancer (Lan et al., 2018). CTLA-4 or CD152, has a short cytoplasmic tail, a signal peptide, a transmembrane domain, and a cellular extracellular ligand-binding domain. CTLA-4 which is a homologue to the CD28 on the T cells, can act as a competitive inhibitor to it by binding to the ligands CD80 or CD86 on the antigen presenting cells (APC), inhibiting T cell activation and raising the T cell response threshold (Lan et al., 2018).

Under physiological conditions, T cells activation needs a stimulatory signal of the interaction between T-cell receptors (TCR) and the MHC, and a co-stimulatory signal of the CD28/B7 (CD86) (Buchbinder, & Desai, 2016).

This binding induces production of IL-2 and other stimulatory cytokines, also improves metabolism, promotes cell cycle progression, up regu-lates cell survival genes, and results in T cell proliferation and differentiation. CTLA-4 is located in an intracellular compartment of resting T cells. CTLA-4 is transported to and expressed on the surface of T cells after CD28 binding activates T cells. This expression of the CTLA-4 molecule is in proportion to the strength of the stimulatory signal received through the TCR (Gönen, 2009).

Tremelimumab and Ipilimumab are a monoclonal antibody against CTLA-4 from the immune check point inhibitor class that are used to remove the blockage of the immune system from fighting the TNBC cells (Santa-Maria et al., 2018).

2.2.4. Gene signatures

Gene expression profiling (gene signature) is often being explored by gene expression studies to eventually recognize molecular targets for treatment. A gene signature is a concept that uses the ex-pression of a small number of genes to predict patient outcome, typically survival or progression (Gönen, 2009). The use of gene signature to classify BC has had a positive effect on diagnosis, prognosis, and therapies for this tumor, with a strong impact on disease-free survival and quality of life for affect-ed patients. These advances have paved the way for molecular studies to be used in the clinical treatment of cancer patients (Santuario-FacioSK et al., 2017). For example, one study studied the gene signature of three coding genes (TCF3, CREB1, and CEP44) and two lncRNAs (NR 023392.1 and NR 048561.1) to effec-tively predict the pCR to neoadjuvant chemotherapy in TNBC patients (Zheng et al., 2019).

Multiple gene signatures have been studied as surrogates of breast cancer immunogenicity in com-bination with TILs. According to immune-related gene expressions, a new proposal divided breast cancer into four groups (immunologic constants of rejection (ICR) ICR1 through ICR4). Defects in the MAPK pathway were strongly linked to an immune-unfavorable phenotype (ICR1), indicating that changes in this pathway are linked to a negative regulation of immune response in breast can-cer (Marra et. al., 2019). In TNBC cells, inhibition of MEK, a key molecule in the MAPK pathway, increased PD-L1 and MHC class I expression, synergizing with PD-L1/PD-1 inhibition in eliciting antitumor im-mune responses in TNBC mouse models. A four-gene signature (HLF, CXCL13, SULT1E1, and GBP1) was discovered to predict an increased number of TILs and better disease-free survival in early stage TNBC in another study (Marra et. al., 2019).

The absence of residual invasive tumor tissue from both the breast and the axilla after neoadju-vant chemotherapy is known as a pathologic complete response (pCR) to NAC (Zheng et al., 2019). Neoadjuvant chemotherapy (NAC) is the use of chemotherapeutic drugs prior to surgical resection to reduce the size of the breast cancer mass and enable the intended surgical procedure to proceed. On the other hand, adjuvant chemotherapy is a form of treatment that is administered after surgery to reduce the chances of the cancer returning (Zheng et al., 2019).

2.2.5. Tumor mutational burden (TMB)

The total number of non synonymous mutations per coding region of a tumor genome is known as the tumor mutational burden (TMB). Initially, whole exome sequencing was used to calculate TMB, but due to the high costs and long processing time of this process, targeted panel sequenc-ing is now being investigated to quantify TMB. A high TMB level has been identified as a genet-ic signature linked to a positive response to immune checkpoint inhibitor therapy. Certain pedia-tric cancers have a very low TMB, about 0.1 mutations per Mb. On the other hand, certain can-cers linked to prolonged exposure to carcinogens, such as malignant melanoma (exposure to ul-traviolet light) or lung cancer (exposure to tobacco smoke), have more than 400 mutations per Mb (Meléndez et al., 2018). Breast cancer has a low mutation rate of 1/Mb, which may explain why it has an intermedi-ate or low immunogenicity (Zheng et al., 2019).

2.2.6. Microsatellite instability (MSI) and mismatch repair (MMR) deficiency

Microsatellites are small tandem repeat DNA sequences of one to tetra base pairs found in both coding and non-coding regions of the human genome. Microsatellites are especially susceptible to replication errors, which are usually corrected by the Mismatch Repair (MMR) method, due to their repeated structure. MMR is a highly conserved cellular mechanism that involves a number of proteins and results in the identification and repair of mismatched bases that occur during DNA replication, genetic recombination, or chemical or physical damage. Small DNA mismatch errors are usually detected during the process of DNA repair, when this process is insufficient it's called defective DNA mismatch repair (dMMR) (Sugie, 2018).

Microsatellite instability (MSI) is a strong mutator phenotype caused by DNA polymerase slippage and characterized by widespread size polymorphisms of microsatellite sequences (Schlötterer, & Harr, 2001; Kurata et al., 2020). MSI is characterized by a decrease or in-crease in repetitive nucleotide sequences, which can contribute to apoptosis evasion, the produc-tion of malignant mutations, and tumorigenesis when triggered by dMMR genes (Ren et al., 2021). MSI is a dMMR marker. Screening for MSI can be done by polymerase chain reaction (PCR) testing for MSI, immuno-histochemical staining (IHC) for altered proteins and next generation sequencing (NGS) technologies from tumor or normal tissue (Schlötterer, & Harr, 2001). As searching for the MSI became a part of the diagnostic process for almost every solid tumor, been studied as a possible prognosticator and therapeutic target in a variety of cancers. The prog-nostic importance of these biomarkers, however, varies by tumor type. dMMR and MSI-H have also been found to be good predictors of immunotherapy response in TNBC (Ren et al., 2021).

2.2.7. Choosing the right chemotherapy to be used in combination with immunotherapy

In the IMpassion130 analysis, nab-paclitaxel was chosen because it allows for less corticoster-oid usage. But better agents, such as anthracyclines, platinum salts, and other taxanes, may be required to improve the immunogenicity of breast cancer (Marra et. al., 2019).

2.2.7.1. Taxanes

TIL recruitment can be increased by taxanes in primary breast cancer. Furthermore, taxanes have been shown to reduce T regulatory and myeloid-derived suppressor cells (MDSCs) in the tumor microenvironment, partially alleviating immunosuppression. We must emphasize that these immunomodulatory effects have only been identified for old generation taxanes (docetaxel and paclitaxel); no preclinical data on nab-paclitaxel effect on the immune system has yet been published (Marra et. al., 2019).

Taxane is a microtubule inhibitor. It enhances the action of tubulin dimers and stabilizes current microtubules while inhibiting their disassembly, promoting microtubule assembly. Thus the late G2 process is stopped, and cell replication is prevented, due to the stability of the microtubules. It is available as an IV formulation that is given over a period of 3 to 24 hours, depending on the indication or procedure. But unfortunately, hypersensitivity reactions and bone marrow suppression are black box warnings for paclitaxel. To prevent anaphylaxis and extreme hypersensitivity reactions, patients should be given corticosteroids, diphenhydramine, and H2 antagonists before the infusion. Alopecia, nausea and vomiting, mucositis, neutropenia, leukopenia, anemia, hypersensitivity reactions, arthralgia, myalgia, fatigue, and peripheral neuropathy are the most common paclitaxel side effects. Patients who experience serious neuropathy should have their dosage decreased by 20% if they develop neuropathy (Farrar et al., 2020).

2.2.7.2. Anthracyclines

The bacteria Streptomyces spp. are used to produce the medication anthracyclines (e.g. Dauno-rubicin and Doxorubicin). Many different mechanisms have been proposed to explain anthracy-clines' cytostatic and cytotoxic effects, including free radical formation, lipid peroxidation, direct membrane effects, and enzyme interactions. 1- Reactive Oxygen Species (ROS): In the presence of cytochrome P450 reductase, NADH dehydrogenase, and xanthine oxidase, redox reactions produce reactive oxygen species. Excess ROS cannot be detoxified, causing oxidative stress, DNA damage, and lipid peroxidation, which leads to cell death. 2- DNA Intercalation: When localized to the nucleus of the cell, anthracyclines have a chromophore moiety that has an interca-lating role and inserts between adjacent base pairs of DNA, inhibiting DNA and RNA synthesis and preventing cell division. 3- DNA Adduct Formation: Formaldehyde-releasing pro-drugs are known to facilitate the formation of adducts between these drugs and DNA. The adducts bind to various transcription factors and cause apoptosis to occur. 4- Enzyme Interaction: The interac-tion of anthracyclines with topoisomerase-II is the most generally accepted mode of action. The ternary complex that results prevents the ds-DNA breaks from re-ligating. As a result, it induces cell growth arrest and apoptosis (Venkatesh et al., 2021).

The mode of administration is usually intravascular or in an injected form and the dose is measured based on body surface area. The most common side effects to Anthracyclines are nau-sea, vomiting, anemia, itching, fatigue, hair loss, change in bowel movements, leukopenia, throm-bocytopenia, red urine, cardiomyopathy, seizures, photosensitivity and myelosuppression. An-thracycline-induced cardiotoxicity is a major cause of morbidity and mortality. New-onset heart failure and/or diagnosis of left ventricular dysfunction in exposed persons are the clinical presen-tation; the most widely used indicator for this side effect is LV ejection fraction. The complica-tions of tissue necrosis caused by anthracycline extravasation are numerous. Extravasation can be treated with dexrazoxane, which is an antidote (Venkatesh et al., 2021).

2.2.7.3. Cyclophosphamide

Cyclophosphamide is a nitrogen mustard with anti-neoplastic properties mediated by DNA alkylation. The drug has no cell-cycle phase preference and metabolizes to an active form hydroxycyclophosphamide by the liver and works by inhibiting protein synthesis by cross-linking DNA and RNA. This cross linking is permanent leading to programmed cell death. Low-dose cyclophosphamide has shown promise in selective immunomodulation of regulatory T cells, whereas high-dose cyclophosphamide is used in the eradication therapy of malignant hematopoietic cells. In the CSF and peripheral blood, the drug reduces the secretion of interferon-gamma and IL-12 while increasing the secretion of Th2 cytokines including IL-4 and IL-10. Hemorrhagic cystitis, amenorrhea, myelosuppression, alopecia, and nausea and vomiting spells have all been identified as side effects from the use of cyclophosphamide. Monitoring the patient's hematologic profile and modifying care as appropriate are recommended to avoid the negative effects of cyclophosphamide toxicity. Patients can take plenty of water, and mesna can be used as a preventative measure against hemorrhagic cystitis (Ogino, & Tadi, 2021).

2.2.7.4. Gemcitabine

Gemcitabine (dFdC) is an analog of deoxycytidine. It is a prodrug that must be phosphorylated by deoxycytidine kinase to become active once it enters the cell. Gemcitabine diphosphate (dFdCTP) and gemcitabine triphosphate (dFdCTP) both inhibit DNA synthesis processes. The most possible mechanism by which gemcitabine induces cell death is the incorporation of dFdCTP into DNA. DNA polymerases are unable to proceed when one more deoxynucleotide is inserted after the gemcitabine nucleotide is incorporated on the end of the elongating DNA strand (Plunkett et al., 1995). Also, it enhances the anti-tumor activity of CD8+ T cells (Homma et al., 2014).

2.2.7.5. Breast cancer vaccines

Cancer vaccines are new therapeutic approach to stimulate the immune system against the cancer cell. They include monovalent vaccines that give the immune system a single tumor-associated antigen (TAA) target and polyvalent peptide vaccines that give the immune system several TAA targets (Vikas et al., 2018). Breast cancer vaccines against shared tumor antigens have been evaluated in multi-ple trials. Some of these peptide and/or protein vaccines were specific for HER-2 or the carbohy-drate antigen Mucin-1, DC-based vaccines specific for HER-2, cell-based (poly-antigen), virus vector vaccines that carry carcinoembryonic antigen (CEA), Mucin-1, and a triad of molecules that induce T cell activation (TRICOM), as well as cell-based (poly-antigen) vaccines that secrete granulocyte-macrophage colony stimulating factor (GM-CSF) (Emens, 2018).

3. Conclusion:

In this paper, we have put the light on the current literature on immunotherapy to present a brief review of the different mechanisms by which the immune system is utilized to eliminate the TNBC. Also, we outlined the different immunotherpies based on these immune mechanisms, to-gether with chemotherapy options that can be chosen for the management regimen.

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