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The Use of Atezolizumab + Nab-Paclitaxel for Women with PD- L1 Positive Advanced Triple-Negative Breast Cancer

Vahideh Beygi Rezagholi[1], Sheby Elsa George[2], Gouthami. U[3]

[1,2,3]PharmD Interns, Department of Pharmacy Practice, Karavali College of Pharmacy, NH-13, Opp. Mangalajyothi, Vamanjoor, Mangalore- 573028 Karnataka, India

Corresponding Author: Sheby Elsa George

ABSTRACT

Triple-negative breast cancer (TNBC) is an uncommon subtype of breast cancer that constitutes 15-20% of cases which has a poorer prognosis and lower survival rates (approximately 18 months or less with available treatments) compared to other types of breast cancer. As the name suggests, TNBC is immunohistologically marked by the lack of expression of factors namely estrogen receptors (ER), progesterone receptors (PR), and lack of overexpression and/or amplification of the human epidermal growth factor receptor 2 (HER2)/NEU gene. TNBC is characterized by high grades of Tumor-Infiltrating lymphocytes (TILs), programmed-death ligand 1 (PD-L1) expression, and cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) as observed in other cancers too. Hence, metastatic TNBC (mTNBC) therapy focuses on the advancement of immune checkpoint inhibitors which block the above immune checkpoint proteins. The use of Atezolizumab (anti-PD-L1) in combination with nab-paclitaxel (chemotherapy agent) has been marked as a relevant advance in the treatment of metastatic, PD-L1-positive TNBC. It is better to consider advanced and approved diagnostic (VENTANA PD-L1 SP142 assay) in patients who get benefit from treatment with Atezolizumab plus nab-paclitaxel.

Keywords: Triple Negative Breast Cancer (TNBC), Atezolizumab, Nab-paclitaxel, Chemotherapy

INTRODUCTION

Among all cancers, Breast Cancer (BC) is the leading malignancy in women and has the second-highest incidence also the fifth-highest mortality rate in both developed and developing countries (Based on 2018 studies, 11.6% new diagnoses and 627,000 deaths).[5,6] A malignant tumor that has developed from cells in the breast commonly called breast cancer, which either begins in the cells of milk-producing glands (the lobules) or the ducts (the passage that drains milk from the lobule to the nipple).[27]

Triple-negative breast cancer (TNBC) is an uncommon subtype of breast cancer that constitutes 15–20% of cases which has a poorer prognosis and lower survival rates(approximately 18 months or less with available treatments) compared to other types of breast cancer.[3,6,7]As the name suggests, TNBC is immunohistologically characterized by the lack of expression of factors namely estrogen receptors (ER), progesterone receptors(PR), and lack overexpression and/ or amplification of the human epidermal growth factor receptor 2 (HER2)/ NEU gene.[4,9] Compared to non-TNBC, the patients with TNBC is more likely to develop metastases of the central nervous system and visceral organs along with quick relapses.[17,26]

The risk factors for TNBC include age; more common in younger patients, race; African Americans, and those with

deleterious BRCA mutations, who encounter a higher risk of metastatic recurrence.[13]

TNBC is characterized by high grades of Tumor-Infiltrating lymphocytes (TILs), programmed-death ligand 1 (PD-L1) expression, and cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) as observed in patients with multiple malignancies, including melanoma, non-small cell lung cancer, and renal cell carcinoma. Hence, metastatic TNBC (mTNBC) therapy focuses on the advancement of immune checkpoint inhibitors which block the above immune checkpoint proteins.[2]

Cytotoxic chemotherapeutic agents such as taxanes and anthracyclines were the established treatment option for the advanced TNBC used over the past two decades.[12] In the past few years, studies show about 20% of patients of TNBC express PD-L1 which presents mainly on tumor-infiltrating immune cells rather than on tumor cells and PD-1, therefore recommendations have emerged important role of anti-PD-L1/anti-PD1 therapy in TNBC patients.[4,8,12]The use of atezolizumab (anti-PD-L1) in combination with nab-paclitaxel (chemotherapy agent) has been marked as a relevant advance in the treatment of metastatic, PD-L1-positive TNBC which received accelerated approval on March 8, 2019, by the FDA based on data from Impassion 130.[9]

Humanized immunoglobulin G1 monoclonal antibody, Atezolizumab disinhibit T cells from attacking TNBC cells by selectively inhibiting the binding of PD-L1 to its receptors PD-1 and B7 in the tumor microenvironment.[1,2]Microtubule inhibitor, Nab-paclitaxel (a nanoparticle albumin-bound paclitaxel) is a chemotherapeutic agent which has efficient immunosuppressive effects and is considered to be a first-line drug used in combination with other biological therapies for the treatment of metastatic breast cancer.[1,9]Combination therapy is preferred over single Anti–PD-L1/PD-1 agent with its efficient synergistic activity by targeting different steps in the cancer immunity cycle, which has been approved by the US Food and Drug Administration and the European Commission for the treatment of PD- L1 positive advanced triple-negative breast cancer.[1,3,6]

Efficacy of Atezolizumab in combination with nab-paclitaxel was compared to nab-paclitaxel and placebo combination in phase III, international, randomized, double-blind, placebo-controlled study, Impassion-130.[]Based on priortaxane use, liver metastases, andPD-L1 status patients were stratified and the primary endpoints assessed include progression-free survival and overall survival.[2]

Classification of TNBC

On presenting breast cancer, we can observe cellular and molecular heterogenecity with numerous genes controlling the process of the disease condition.[15] Breast cancer, based on the gene expression can be categorized into 4 main groups which are": luminal subtype (classified into Luminal A and Luminal B, and is presented by estrogen receptor(ER) gene expression and cytokeratins (CK)).[14,15]

The HER2 subtype (characterized by HER2 gene amplification at 17q22.24 including ERBB2 and GRB7), the basal-like subtype (showing positivity for basal and myoepithelial markers and lack of hormone receptors and HER2 gene amplification with high expression of CK 5/6 and 17, laminin and fatty acid-binding protein 7) and "normal breast-like" subtype (express characteristic genes of basal epithelial and adipose cells).[14,15]

Pathologic features of PD L1 TNBC

The structure of a normal breast is made of stratified epithelium which comprises two different cell populations, epithelial and myoepithelial, and is bounded by a basement membrane.[19]A hypothesis states that the generation of cellular heterogeneity in breast lesions depends on the underlying developmental program of

the normal breast and that breast carcinoma heterogeneity could arise from the neoplastic transformation of either of the stratified epithelium or even from a stem cell which is potent to differentiate into epithelial or myoepithelial cells.[20] Neoplastic transformation happens at different points of maturation other than all breast cancer subtypes which derive from the same type of cell and this kind of transformation could take place in the immature/ basal cell and this tumor cell would acquire luminal cell characteristics or remain undifferentiated.[17]

Breast cancer susceptibility gene 1 (BRCA1) (required for the conversion of ER-negative cells to ER-positive) and breast cancer susceptibility gene 2 (BRCA2) are the two major genes associated with susceptibility to breast and ovarian cancer which is essential in the homologous recombination (HR) process. 60-85% risk of breast cancer arises from the mutations in any of these genes. BRCA2 has significance in DNA recombination and repair processes where BRCA1 is associated with DNA repair, transcriptional regulation, and chromatin remodelling BRCA dysfunction can be an important mechanism in TNBC development. Cells that lack either of these genes are not able to repair DNA double-strand breaks by HR and would bring about chromosome translocation and genomic instability.[15]

PD-L1 expression and other prognostic factors do not show any relationship whereas a statistically significant association was observed between the tumoral PD-L1 positivity and parameters such as histological type and Ki 67 index in TNBC. The tumor and the tumor microenvironment of TNBC have a marked PD-L1 expression rate.[18]

TNBCs are typically characterized by ductal invasive carcinoma, a high histologic grade with central necrotic zones, rare medullary and elevated mitotic count, tumor necrosis, pushing margin of invasion, larger tumor size, and axillary node involvement.[15] Fibrosis with a pronounced degree of hyalinization is observed in non-TNBCs while Triple-negative tumors often demonstrate a cellular fibrous proliferation with differently sized blood vessels, intratumoral lymphocytic inflammatory infiltrate and a perilobular lymphocytic infiltrate in breast tissue beside the tumor.[17]

Biomarkers

Advancement in the treatment of TNBC patients was made possible by the identification of biomarkers and their acceptance, which serves as prognostic aids as well as potential therapeutic targets.[17] Biomarkers associated with TNBC include Androgen Receptor, Epidermal Growth Factor Receptor, Fibroblast Growth Factor/Receptor, Vascular Endothelial Growth Factor/ Receptor.

Proliferative activity in ER-positive tumors is inhibited by androgen receptors whereas tumorigenesis in ER-negative tumors is independently promoted. AR acts as a mediator in the activation of the WNT and HER2 signaling pathways (ligand-dependent). Type I transmembrane tyrosine kinase, EGFR, and its pathway tends to exhibit Dysregulation in numerous epithelial tumors, with a frequency of 50% in TNBC and 65% to 72% in basal-like carcinomas in some studies.[21]

TNBCs are known to have marked levels of vascular endothelial growth factor (VEGF), as neoangiogenesis is crucial to tumor progression and regardless of tumor stage these levels correlate with poor outcome.[22] Fibroblast Growth Factor/ Receptor has been identified in triple-negative cell lines and recruits macrophages to the tumor microenvironment through amplification. There is a strong Recruitment of macrophages that leads to the promotion of cell invasion, angiogenesis, and immune suppression and macrophage density are strongly correlated with poor prognosis.[23] mTORC1 and MTORC2 are the two forms of a serine-threonine protein kinase mTOR and are regulated through the PI3K/AKT pathway. The downstream effects of the

activation of this complex have been associated with cellular transformation, and their overexpression has been linked to a poor prognosis in cancer. evidence suggests that mTOR inhibitors may have a role in TNBCs. [24,25] A phase II study showed that the addition of an mTOR inhibitor to standard chemotherapy was well tolerated in TNBC and resulted in a slight improvement in the 12-week response rate.[8]

Other biomarkers associated with TNBC and basal phenotype includes stem cell-related proteins (nestin and p63), other receptor tyrosine kinases (MET, KIT), and tumor-associated stromal proteins such as matrix metalloproteases.[15]

Pharmacotherapy of TNBC

A sequence of single-line agents is chosen for the treatment of metastatic TNBC. In combination therapy, response rates are more which includes surgery, radiation therapy, and chemotherapy are preferred in patients with fast disease progression required to reduce the number of tumor cells for symptom management.[13] For patients diagnosed with early TNBC (stage 1-3), anthracyclines and taxanes are actively promoted as neoadjuvant chemotherapy where TNBC is treated with chemotherapy before surgery. Anthracyclines such as doxorubicin have a 35–50% response rate; although due to the risk of cardiomyopathy and reduced ejection fraction long-term administration is restricted. In metastatic breast cancer, Taxanes including docetaxeland paclitaxel are active with a 25-35% response and survival rate in comparison to all breast cancer subtypes formerly treated with an anthracycline.[13]

A BRCA mutation is relevant to consider in metastatic breast cancer. PARP (The poly ADP-ribose polymerase) inhibitors such as olaparib, talazoparib have been approved to treat people with BRCA1 or BRCA2 mutation. PARP enzyme corrects the DNA damage in both healthy and cancer cells. Some studies have shown that the drugs which are involved to inhibit the PARP enzyme make it difficult for cancer cells with BRCA mutation to fix DNA damage.[13]

Eribulin, capecitabine, vinorelbine, and gemcitabine are other chemotherapy agents with effects in metastatic TNBC. Following the oral administration prodrug, capecitabine is converted to 5-fluorouracil and is often preferred due to the absence of alopecia as a side effect. Capecitabine and eribulin overall have a similar effect. Vinorelbine is a semisynthetic vinblastine derivative that inhibits microtubule formation by binding to tubulin. It has no much evaluating effect in TNBC, though studies including single therapy of vinorelbine have shown outcome in particularly patients with HER2-negative metastatic breast cancer. Gemcitabine is a pyrimidine antimetabolite that is usually used in combination with carboplatin, which hinders DNA synthesis by the inhibition of DNA polymerase and ribonucleotide reductase.

Atezolizumab has a good safety profile and clinical efficacy in patients with TNBC and specifically targets PD-L1 to prevent interactions with its receptors programmed death-1 and B7, advised dose of atezolizumab in the treatment of metastatic TNBC is 840 mg administered on days 1 and 15 for each 28-day cycle. Atezolizumab in combination with nanoparticle albumin-bound paclitaxel thereafter referred to as nab-paclitaxel which has potential immunosuppressive effects and suggested dose is 125 mg administered on days 1, 8, and 15 of each cycle.[6]

Pharmacology and Administration of Atezolizumab

Atezolizumab has been structured as, humanized immunoglobulin (IgG4) monoclonal antibody, which includes two long chains (448 amino acids) and two short chains (214 amino acids), affects PD-L1 in the tumor microenvironment and reactivates T cells by inhibiting the binding of PD-L1 to PD-1 and B7.1.[1,2] Atezolizumab as a

Chemotherapy agent has been proved to have an acceptable safety and efficacy in profile and therapy in patients with TNBC by enhancing the tumor antigen release and antitumor responses to immune checkpoint inhibition.[11] In the process of therapy of metastatic TNBC the accepted dose of atezolizumab is 840 mg which can be administered every 28-day cycle on 1st and 15th of each cycle.[15] The acceptable route of administration for atezolizumab as an infusion and the onset infusion should be administered during 60 min accompanied by infusions over 30 min if the first infusion is tolerated. Steady state will be reached within 6-9 weeks after getting multiple doses of the drug. Atezolizumab has a clearance of 0.20 L/day, the volume of distribution is 6.7 L, and the terminal half-life is approximately 27 days. Atezolizumab should be administered before nab-paclitaxel but not as an IV push or bolus.[13]

Pharmacology and Administration of Nab-Paclitaxel

Nab-paclitaxel has been characterized by highly lipophilic and insoluble in water drug and is an albumin-bound type of paclitaxel. The paclitaxel is considered as nanoparticles with a size of nearly 130 nanometres which is bounded to a protein called human albumin. Ratio of paclitaxel and albumin is 1:9 in each vial of nab-paclitaxel. In comparison between nab-paclitaxel and paclitaxel (non-protein-bound form), Nab-paclitaxel is considered as a solvent-free type of drug, unlike paclitaxel which requires a solubilizer like Cremaphor EL for intravenous administration. Studies show the presence of enhanced hypersensitivity reactions along with the use of solubilizer in paclitaxel. So, premedication therapy of corticosteroids and antihistamines has been suggested to decrease the risk of reaction. Since nab-paclitaxel is solvent-free, there are few occurrences of hypersensitivity reactions in comparison with paclitaxel. So, nab-paclitaxel is administered in the absence of prior medication with corticosteroids. Immunosuppressive effects of nab-paclitaxel's dose in the therapy of TNBC for each 28-day cycle is 100mg/m2 on days 1, 8, and 15.[13]

Combination Therapy with Atezolizumab And Nab-Paclitaxel in TNBC

Based on studies, using of atezolizumab as a chemotherapy agent and nab-paclitaxel as an immunosuppressant agent has been investigated in combination therapy of triple-negative breast cancer. Combination of atezolizumab with nanoparticle albumin-bound paclitaxel (nab-paclitaxel) with nab-paclitaxel has been approved by US Food and Drug Administration and also, the European Union as an efficient therapy in patients with mTNBC or unresectable locally advanced with tumors shows expression ≥1% of PD-L1.[2,3,6] Although,Anti–PD-L1/PD-1 agents like nab-paclitaxel act as effective agents in patients with mTNBC clinically, but their use as a single-drug therapy shows low response rates in compare to combination therapy. Combination of nab-paclitaxel as immunosuppressant agent with chemotherapy agents like atezolizumab affect several steps in the cancer immunity cycle by implementing synergistic activity.[1] As mentioned, in administration of nab-paclitaxel using of steroid premedication as a solvent is not required,so albumin-bound of paclitaxel has presented efficient result as a drug in combination with atezulizumab and is a reasonable associate for trialing chemoimmunotherapy combinations. In patients with clinical benefit in therapy atezulizumab could be continued with or without nab-paclitaxel and nab-paclitaxel could be discontinued without of atezolizumab. Intravenous atezolizumab, 800 mg, on days 1 and 15 of each cycle every 2 weeks and intravenous nab-paclitaxel, 125 mg/m2, on days 1, 8, and 15 of each cycle (3 weeks on, 1 week off) has been recommended as acceptable dose and route of administration in patients who received.[1]

Adverse Drug Reactions and ADR of Special Interest

Atezolizumab plus nab-paclitaxel Combination therapy was found to have a similar frequency of immune-related AES and safety profile that is consistent with the known adverse effects of other chemotherapy agents or as a single agent.[4] Treatment-Related and Immune-Related Grade 3/4 Adverse Events (AEs) includes neutropenia, peripheral neuropathies, nausea, fatigue, and alopecia and were able to manage by disruptions or discontinuation of the treatment.[1,4] Urinary tract infection, dyspnea, and pyrexia are the most frequent serious adverse reaction of this combination therapy.[9] Elevated AST, ALT, increased Pneumonitis, drug reaction with eosinophilia, Type 1 diabetes mellitus, and colitis were the adverse events of special interest.[1]

CONCLUSION

An article published in November 2018, showed the rousing results of the phase III study that the inclusion of atezolizumab to nab-paclitaxel as the first-line agent in the treatment of patients with advanced TNBC revealed remarkably prolonged OS and PFS, compared with those obtained with nab-paclitaxel alone, which was the great finding in the first-line treatment of this malignancy.[11] In HRQoL, physical, role, and cognitive functioning, Atezolizumab plus nab-paclitaxel had correspondent outcomes compared with placebo plus nab-paclitaxel in IMpassion130.[2]

Since routine testing for PD-L1 immune-cell expression is not resectable, it is better to consider advanced and approved diagnostic (VENTANA PD-L1 SP142 assay) in patients who get benefit from treatment with atezolizumab plus nab-paclitaxel.[3] For patients with metastatic triple-negative breast cancer, it is important to consider PD-L1 expression status on tumor-infiltrating immune cells to notify treatment choices.[4] It is relevant to consider the economic evaluation of high-cost drugs to minimize the financial burdens for patients with cancer and to completely make use of limited medical resources.[11]

For the treatment of patients with metastatic TNBC whose tumors express PD-L1, atezolizumab plus nab-paclitaxel exhibits an appropriate benefit-risk profile. So, as a result, combination therapy with AnP shows logically likely an acceptable safety result in patients with TNBC.[9]

Till now the only immune checkpoint inhibitor approved for breast cancer is atezolizumab. Many cost-effectiveness studies were conducted regarding the atezolizumab as a first-line agent in other cancer patients such as lung cancer.[11]Some studies implied that AnP (atezolizumab plus nab-paclitaxel) have more clinical outcome when compared to nab-paclitaxel as the first-line therapy for advanced TNBC and inclusion of atezolizumab with nab-paclitaxel would not be a cost-effective strategy, to improve this minimizing the price of atezolizumab may be a possible measure. For effective treatment options of TNBC, clinical decision-makers need to consider decisions.[11]

Fortunately, several types of research are in progress in the development of new immunotherapy methods in TNBC to achieve the goal of therapy, especially in patients who are in the early stage of TNBC. Hereof, challenging outcomes issued by IMpassion130 caused the development of more trials in the investigation of PD-1 or PD-L1 inhibitors in patients with the initial phase of TNBC and efficacy of therapy in combination with other chemotherapy agents. With the help of new trials and studies like personalized and specialized cancer vaccines, T-cell stimulatory molecules agonist and bispecific antibodies binding tumor antigens andimmune cell surface proteins, there is vast progression and development in the survival of TNBC patients.

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