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REVIEW ARTICLE

The Renaissance of Interest in Breast Cancer Treatment by PD1/PDL1 Checkpoint Inhibitors

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ABSTRACT

Background: Breast cancer is the most common cancer in females. It is the main cause of cancer-related deaths in women. Despite the benefit of using standard treatment modalities like chemotherapy, anti-Her-2 monoclonal antibodies, and hormonal therapy in the prognosis of breast cancer, 15% of breast cancer patients will have metastases and die. Grand effort has been given to understand breast cancer oncogenesis which helped with the approval of several drugs targeting cancer cells like immune therapy. The immune system has a significant role in the behavior of cancer. Contemporary, immunotherapy development through the immune checkpoint blockers demonstrated promising antitumor effects in multiple cancers that don't respond to conventional treatments. Despite promising results, a good response is seen only in part of patients, and there is still a need for a monotherapy modality with curative ability.

Conclusions:PD-1/L1 pathway aids the development and progression of cancer. It promotes cancer by negatively regulating the immune responses mediated by T-cells and inhibiting proliferation, migration, and effector function of T cells. PD-1/L1 blockade treatment showed a promising effect in cancer immunotherapy. This type of immunotherapy is significantly effective in malignancies containing a high expression of PDL-1/2.

Keywords: Breast cancer, PD-1 PD-L1, Inhibitors, Immune response.

INTRODUCTION

Breast cancer is the most common cancer in females. It is the main cause of cancer-related deaths in women [1]. Despite the benefit of using standard treatment modalities like chemotherapy, anti-Her-2 monoclonal antibodies, and hormonal therapy in the prognosis of breast cancer, 15% of breast cancer patients will have metastases and die [2]. Grand effort has been given to understand breast cancer oncogenesis which helped with the approval of several drugs targeting cancer cells like immune therapy [3]. The tumor microenvironment is considered as a reflection of the survival, progression, and invasion or metastasis of cancer. The cancer TAAs (Tumor Associated Antigens) for example; epidermal growth factor receptors (HER2), the tumor suppressor protein (p53), and telomerase reverse transcriptase, are recognized by the immune system as self-antigens, while the immune system has protective mechanisms for preventing recognition of self-tissue antigens and the immunologic destruction [4]. Tumors also have other mechanisms for escaping immune surveillance, such as: low-level expression of MHC class I molecules [4], lack of expression of B7 (CD80/CD86) costimulatory molecules [4], production of cytokines that stimulate the attraction of immune-suppressor cells [5], and ineffective processing and presentation of self-antigens by 'professional' antigen-presenting cells (APC) [4].These mechanisms provide some explanation for why treatment modalities that target TAAs expressed on normal cells in clinical trials generally do not induce strong protective immunity. Identification of new TAAs that are not expressed on normal cells provide a reasonable alternative particularly if combined with potent immunotherapeutic platforms because these antigens are less likely to be subject to the autoimmune response and thus may be better immunogens [4]. Great attention has been given to the PD-1-PD-L1 axis as new therapeutic aims for a

variety of malignancies. There are many ongoing trials to evaluate the value of immunotherapy in blocking the PD-1/PD-L1 axis in breast cancer patients [6]. In this review, we spotlight the improvement of PD-1 and PD-L1 inhibitors in treatment of breast cancer until now.

❖ **History of PD1 Immunotherapy**

PD-1 was discovered in 1992 by Ishida et al. 1992 who first reported that PD-1 can bring a classical type of programmed cell death [7]. In 1999, other researchers verified that PD-1-knockout mice showed lupus-like autoimmune conditions, meaning that PD-1 performs as an immune checkpoint [8]. Later, in 2014, the Food and Drug Administration (FDA) approved the first anti-PD1 monoclonal antibody, nivolumab, as a second-line treatment for metastatic or unresectable melanoma [9]. Subsequently, the FDA approved numerous other anti-PD-1/L1 antibodies till June 2020 for cancer therapy. The FDA approved nivolumab (OPDIVO, Bristol-Myers Squibb Co.) for advanced unresectable, metastatic, or recurrent esophageal squamous cell carcinoma (ESCC) after preceding platinum- and fluoropyrimidine-based chemotherapy [10]. In Japan, atezolizumab was approved as the first immune checkpoint inhibitor for the PD-L1-positive triple-negative breast cancer [6].

❖ **Immune Checkpoint Inhibitors Mechanisms of Action**

The normal immune system can create a complex series of mechanisms to identify and eliminate cancer cells. These mechanisms guard against the growth of malignancy but can endorse the selection of tumor cells, which are able to escape the host's immune response [10]. PD-1 and other Immune checkpoints are typical control pathways in immune cells, which control overactivity of the immune system. PD-1 is one of the CD28 group. It is an inhibitory receptor expressed on activated B cells, T cells, and regulatory T cells (Tregs), macrophages, and natural killer (NK) cells. This inhibitory receptor obtains two binding ligands, PDL-1 and PDL-2 (B7 family) which are expressed on B cells, T cells, dendritic cells, macrophages, and many other cells [9]. PD-1 binds and becomes clustered with T cell receptors (TCRs). Then it recruits the phosphatase SHP2 (Src homology 2 domain-containing tyrosine phosphatase 2) through its immunoreceptor tyrosine-based switch motif, which dephosphorylates the proximal TCR signaling molecules and suppresses T cell activation [12].

❖ **A rationale to support immunotherapy in breast cancer.**

Monoclonal antibodies targeted at HER2, like trastuzumab and pertuzumab mechanism of action partially involves the immune system. The use of these monoclonal antibodies improved survival in HER2-positive breast cancer [13] Trastuzumab binds to the HER2 extracellular domain and creates its antitumor effect when blocking HER2 cleavage. It stimulates antibody-dependent, cell-mediated cytotoxicity and inhibits ligand-independent, HER2-mediated mitogenic signaling [14]. Then, multiple immune response-related variables exhibited a distinct predictive and prognostic value for the chemotherapeutic response. For instance, TILs showed a positive prognostic effect in survival and also could predict pathological response to neoadjuvant chemotherapy in triple-negative breast cancer [15]. After that, the PD-L1 which correlates with the TILs, hormonal receptor-negative, high grade, young age, TNBC subtypes, HER2 positive is expressed in BC. Subsequently, PD-L1 expression was connected to a higher rate of complete response to neoadjuvant chemotherapeutic agents and a good outcome including distinct immune response in the microenvironment of the tumor [13**].**

❖ **Checkpoint inhibitors of PD-1/PD-L1 in the management Breast Cancer**

Immunotherapies have the ability to produce long-lasting responses in numeral solid and hematologic malignancies. Breast cancer has a low immune sensitivity. This is related to the low mutation burden which is the total number of mutations per coding area of a tumor genome of breast cancer. Yarchoan et al. showed a distinct correlation between the objective response rate to PD-1 inhibition and the tumor mutational burden [16]. However, triple-negative, Her-2 enriched biologic subtypes and advanced to metastatic stages are considered the most aggressive as the mutation burden found to be high in such situations. There are multiple ongoing clinical trials focused on breast cancer that evaluates various combinations between anti-PD-1/PD-L1 inhibitors and other agents. (Table 1)

❖ **PD-1/L1 Inhibitors Drawbacks in Cancer Management**

Depending on their mechanism of action, immunotherapies lead to distinctive toxicity profiles. The toxicities produced by immunotherapies need significant management usually including steroids and immune-modulating therapy **(Table 2)** [16]. **PD-1 and its ligand PD-L1** inhibit the antitumor function of T-cell. This function can lead to a significant constellation of organ-specific inflammatory side effects like

pneumonitis [17].The most common adverse reactions of **Avelumab** which are reported in ≥20% of patients with metastatic Merkel cell carcinoma are rash, peripheral edema, infusion-related reaction, musculoskeletal pain, fatigue, decreased appetite, nausea, and diarrhea while the most common adverse reactions reported in ≥20% of patients with locally advanced or metastatic urothelial carcinoma are musculoskeletal pain, fatigue, nausea, decreased appetite, urinary tract infection and infusion-related reaction. The most common adverse reactions of **KEYTRUDAc** which are reported in ≥20% of patients are nausea, decreased appetite, diarrhea, constipation, rash, pruritus, fatigue, musculoskeletal pain, pyrexia, dyspnea, and cough [16].The most common adverse reactions of **OPDIVO** as a single agent, reported in ≥20% of patients, are decreased appetite, nausea, diarrhea, constipation, abdominal pain, fatigue, musculoskeletal pain, asthenia, back pain, arthralgia, headache, pyrexia, upper respiratory tract infection, cough, dyspnea, rash, and pruritus. While Its most common adverse effects if combined with ipilimumab for melanoma treatment, reported in ≥20% of patients, are nausea, vomiting, diarrhea, dyspnea, rash, fatigue and pyrexia while for renal cell carcinoma treatment are arthralgia, musculoskeletal pain, fatigue, decreased appetite, nausea, diarrhea, pyrexia, rash, pruritus, and cough [16].

❖ **Toxicity of PD1-PDL1 inhibitors versus chemotherapy.**

Immunotherapy and chemotherapy are two commonly used cancer treatment modalities. Both types stop the growth of cancer cells. Although they have the same goal, the way they accomplish it is different.Immunotherapy's potential side effects usually results from an overstimulated or misdirected immune response while chemotherapy is intended to attack rapidly dividing cells (interference with DNA synthesis) within the body ,which may include both cancerous and non-cancerous cells ,such as mucosa and hair follicles . **(Table 3)**

Table1. Published clinical trials using PD (L)-1 inhibitors in breast cancers (14)

Anti-PD(L)-1	Ph.	Single (S) or Combination	Study Title	Conditions or Disease	Treatment Line	Ref.
Atezolizumab (Tecentriq®)	III	Nab-paclitaxel	IMPASSION-130	LA or M+ TNBC	1 L	Schmid NEJM 2018 Schmid ASCO 2019
Pembrolizumab (Keytruda®)	III	S	KEYNOTE-119	M+ TNBC	2 L or 3 L	Merck press release
Pembrolizumab	II-R	Standard Chemo	I-SPY 2 trial	LA TNBC	Neo-adj	Nanda ASCO 2017
Durvalumab (Imfizi®)	II-R	Nab-paclitaxel + standard EC	GeparNuevo	LA TNBC (cT2-cT4a-d)	Neo-adj	Loibl Annals Oncol 2019
Nivolumab (Opdivo®)	II-R	Doxo or Cyclo or RT (3*8 Gy)	TONIC	M+ TNBC	1 L to ≥3 L	Voorwerk Nature Med 2019
Avelumab (Bavencio®)	Ib	S	JAVELIN	M+ BC	≥1 L	Breast Cancer Res Treat. 2018

Ph. = phase, IIR = phase II Randomized, TNBC: Triple Negative Breast Cancer, LA = Locally Advanced, M+ = metastatic, ORR = Objective Response Rate, DOR = Duration of Response, PFS = Progression-Free-Survival, OS = Overall Survival, L = Line; mo. = months, NR = Not Reached, gBRCAm = germline BRCA-mutated;

Table2. Overview of Common Checkpoint Inhibitor Toxicities

TOXICITY	BASELINE MONITORING	PRESENTATION	MANAGEMENT
Dermatologic	-Complete Skin and mucus membrane examination. -Obtain history of immune-related Skin disorders.	-Maculo-papular/ papulo-pustular rash -Dermal hypersensitivity reaction	**-Grade 1:** emollients, topical corticosteroids, and/or oral histamines **-Grade 2:** high-potency topical corticosteroids and/or oral steroids **-Grade 3-4:** hold ICI; treat with systemic 1-2 mg/kg/d steroids; dermatology consultation

TOXICITY	BASELINE MONITORING	PRESENTATION	MANAGEMENT
Endocrine Thyroid	TSH, free T4 at baseline and every 4-6 wk. on ICI	Hypothyroidism Hyperthyroidism Myxedema	-**Asymptomatic** hypothyroidism: thyroid hormone replacement if TSH >10 mIU/L -**Symptomatic hypothyroidism**: thyroid hormone replacement -**Hyperthyroidism:** if symptomatic, consider endocrine consultation and propranolol for symptom control
GI Colitis		Diarrhea Fever Cramping Urgency Abdominal pain	-**Grade ≥2:** hold ICI until recovery to grade ≤1; evaluate for infection; start 1-2 mg/kg/d steroids; gastroenterology consult -If **no response within 3-5 d**, consider adding infliximab -**In refractory cases** or cases with a contraindication to infliximab, vedolizumab can be used; earlier initiation of biologic therapy may lead to improved outcomes

Table 3. Toxicity of PD1-PDL1 inhibitors versus chemotherapy.

Side effects	Chemotherapy	Checkpoint inhibitors
Common /general	Fatigue nausea hair loss mouth sores	Reaction at injection site flue like symptoms autoimmune response
GIT	Diarrhea “irinotecan “	Ulcerative colitis Chron’s disease
Muscle	-------	myositis
Bones	-------	Arthritis
Nerves	Neuropathy	Neuropathy
Liver	Disturbed liver function – hepatitis	Autoimmune hepatitis
Lung	Rare pneumonitis “bleomycin”	Pneumonitis
Skin	Hand foot syndrome “ fluropyramidins “	Rash Pruritus Vitiligo

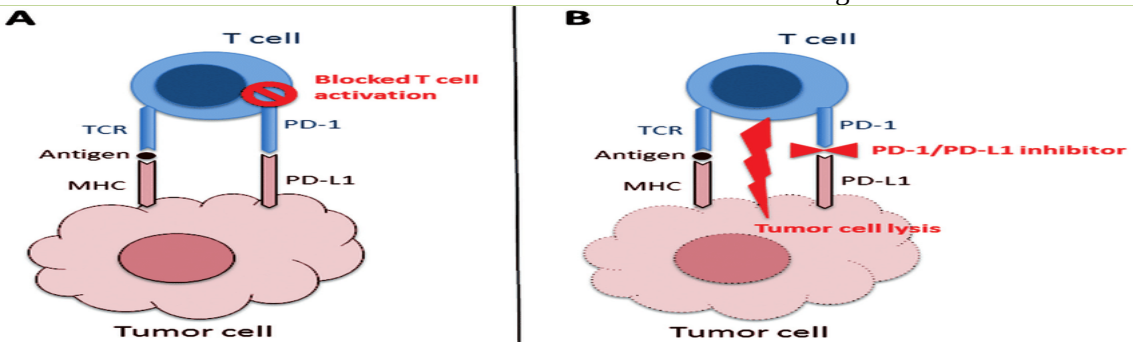

Figure (1): Interaction of cytotoxic T lymphocytes with tumor cells. A: Tumor cells present antigens on major histocompatibility complex (MHC) molecules to the T-cell receptor (TCR). T-cell activation is inhibited by an interaction of the co-inhibitory receptor programmed death 1 (PD-1; expressed on T-cells) with its ligand programmed death ligand 1 (PD-L1; expressed on tumor cells). B: Monoclonal antibodies targeting PD-1 such as nivolumab or pembrolizumab or PD-L1 such as atezolizumab block the inhibitory PD-1/PD-L1 interaction and thus facilitate T-cell-mediated tumor cell lysis.

CONCLUSION

PD-1/L1 pathway aids the development and progression of cancer. It promotes cancer by negatively regulating the immune responses mediated by T-cells and inhibiting proliferation, migration, and effector function of T cells. PD-1/L1 blockade treatment showed a promising effect in cancer immunotherapy. This type of immunotherapy is significantly effective in malignancies containing a high expression of PDL-1/2.

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