A Review Immuno Oncology: Ctla-4, Pd-1 and Pd-L1   Immune Check Point Inhibitors

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ABSTRACT: Cancer is an intricate disease with unusual cell growth in the body which causes over 10 million deaths worldwide as of 2020 as per WHO.[1] Immunotherapy is a ground breaking option for the treatment of cancer patients. Immunotherapy, which stimulates the body's immune system, has received a lot of attention in recent years due to its significant effects. In patients with advanced disease, cancer immunotherapy has had long-term effects not seen with conventional treatment.[2] The FDA has licensed and approved the use of immune checkpoint inhibitors, cytokines including interleukin 2 (IL-2) and interferon-alpha (IFN), and the cancer vaccine sipuleucel-T for the treatment of various malignancies. The most enhanced approach in cancer immunotherapy is Immune checkpoint inhibitors. The results of many tumours have already significantly improved since anti-cytotoxic T-lymphocyte-associated protein-4 (CTLA-4) and anti-programmed cell death protein-1 (PD-1) antibodies were approved for human therapy.[3] Immunotherapies target the tumour indirectly by enhancing the anti-tumor immune responses that naturally develop in many patients, in contrast to radiation and chemotherapy, which try to directly interfere with tumour cell growth and survival. This review will focus on mode of action, efficacy, adverse events of treatment and future approaches of CTLA-4, PD-1 and PD-L1 Immune checkpoint inhibitors.

KEYWORDS: Cancer Immunotherapy, CTLA-4, PD-1, PD-L1, Immune checkpoint inhibitors

I. INTRODUCTION

Immunotherapy is a type of cancer therapy that has transformed the treatment of many tumors by enhancing the body's natural defenses against malignancy. In addition to the conventional methods of surgery, radiotherapy, chemotherapy, and targeted therapy, the results of recent clinical trials using novel immunotherapy strategies, such as immune checkpoint blockade, have clearly established immunotherapy as an important method of treatment for cancer.[4]

The immune system is typically considered to be made up of innate and adaptive systems, although this is a simplification because these systems have overlapping activities and are closely linked. Dendritic cells, Natural killer cells (NK cells), macrophages, neutrophils, eosinophils, basophils, and mast cells make up the innate immune system.[5] Innate immune cells serve as the initial line of defense against foreign antigens because they are not previously required to be stimulated by antigens. The adaptive immune system, which consists of B lymphocytes, CD4+ helper T lymphocytes, and CD8+ cytotoxic T lymphocytes (CTLs), requires a structured exposure by antigen-presenting cells (APCs) to be activated. Antigen-specific T- and B-cell lymphocytes are produced by the adaptive immune system.[6]

The immune system helps to prevent cancers in three distinct ways. First, by removing or reducing viral infections, the immune system can defend the host from viral oncogenesis. Second, the immune system eliminates the inflammatory microenvironment that promotes carcinogenesis by promptly removing infections and inflammation brought on by pathogens. Third, tumor cells can be precisely identified and destroyed by the immune system based on the production of tumor-specific antigens; this function effectively comes under the category of cancer immune surveillance.[7-9] Based on the development of abnormal surface protein profiles, the immune system recognizes malignant and premalignant tumours in this process. It eliminates a lot of them through a variety of processes that involve cytokine production from immune cells that are nearby tumors.[10]

Cancer cells can evade being eliminated by the immune system because genetic changes in

cancer cells make them less detectable to the immune system. Tumor immune escape can arise through intrinsic or extrinsic pathways.[11] The intrinsic processes include alterations in tumors limited antigen expression in the early stages of tumor formation, loss of epitopes, the physical barrier preventing effector cells from penetrating solid tumors, loss of antigen presentation, and the production of immune inhibitory signals such as immune checkpoints.[12] The host immune system, on the other hand, contributes tumor extrinsic mechanisms such as immune tolerance, anergy of tumor-specific T cells, synthesis of soluble ligands that restrict lymphocyte activation, and impairments of specialized APC antigen presentation and maturation. Targeting important immune checkpoints in demanding malignancies is one therapeutic context in which the idea of immunological escape is now being used.[13]

IMMUNECHECKPOINT INHIBITORS

Checkpoint blockade is an approach for inducing antitumor immune responses that involves shutting down immune suppressive pathways that have been triggered by tumour cells. Immunotherapies, especially immune checkpoint blockers (ICBs), are a recognized therapeutic approach for the treatment of cancer.[14] Numerous cancers, including melanoma, Urothelial carcinoma, renal cell carcinoma, and head and neck squamous cell carcinoma, can be treated with these drugs.[15] By removing the "brakes" that control T lymphocytes, which are the primary cells responsible for activating an immune response to cancer, ICBs indirectly affect cancer cells. ICBs are a well-known form of immunotherapy that particularly targets immunological checkpoints, including cytotoxic T lymphocyte-associated antigen-4 (CTLA-4), programmed cell death-1 (PD-1), and programmed cell death ligand-1 (PD-L1). Inhibition of these immune checkpoint molecules inhibits the down regulation of immune cells, resulting in enhanced T cell activity and, eventually, improved anticancer immunity. Ipilimumab, a CTLA-4 inhibitor, is approved to treat advanced or metastatic melanoma.[16] Both PD-1 inhibitors, nivolumab and Pembrolizumab, are authorized to treat patients with refractory non-small cell lung cancer as well as those with advanced or metastatic melanoma. Furthermore, the combination of Ipilimumab and nivolumab has been approved in patients with BRAF WT metastatic or unrespectable melanoma. CTLA-4 and PD-1 play very different functions in suppressing immunological responses, including anticancer responses. CTLA-4 is considered to regulate T-cell proliferation early in an immunological response, largely in lymph nodes, whereas PD-1 suppresses T cells later in an immune response, primarily in peripheral tissue.[17-19]
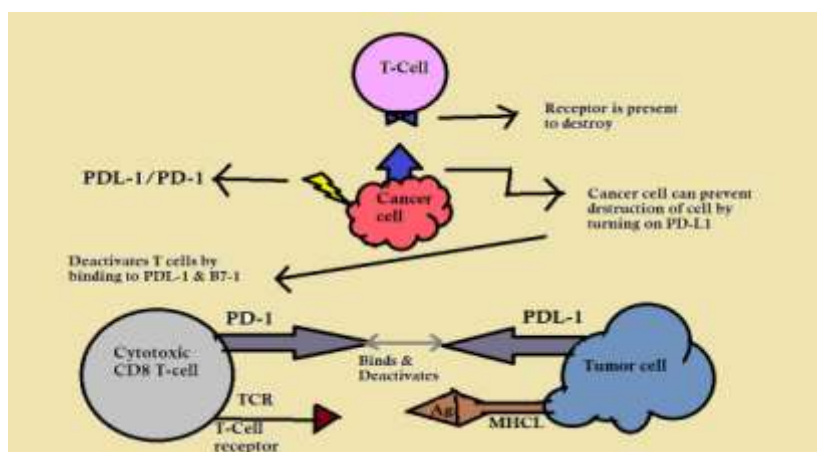

Figure 1: Cancer immunity and mechanism of Immune checkpoint inhibitors

Cytotoxic T-Lymphocyte Associated Protein (CTLA-4)

In the late 1980s, an immunoglobin with an as-yet-unknown function that was largely detected on CD4+ or CD8+ T-lymphocytes was named CTLA-4. High amounts of CTLA-4 are necessary for maintaining particular subsets of T-regulatory cells, according to several research.[20] CTLA-4, like CD28, binds B7 receptors on APCs. As an alternative, it initiates inhibiting actions upon binding, such as cell cycle arrest and reduced cytokine production. More significantly, some molecules of the B7 receptor have much higher CTLA-4 binding affinity than CD28, with one

CTLA-4 receptor capable of simultaneously binding up to eight B7 molecules.[21] Thus, normal T-cells engage in a balancing act between CTLA-4/B7 inhibitory signals and CD28/B7 mediated activating signals to aid the launch of robust killing and also to serve to prevent extended activation when inappropriate.[22]

CTLA-4 is regulated by its location within the cell. CTLA-4 is mostly found in the intracellular compartment of naive T lymphocytes that are at rest. By causing the exocytosis of vesicles carrying CTLA-4, stimulatory signals brought on by both TCR and CD28:B7 binding cause the up regulation of CTLA-4 on the cell surface.[23] A graded feedback loop governs how this mechanism works, with greater TCR signaling causing more CTLA-4 to translocate to the cell surface. Full T cell activation is blocked in the event of a net negative signal by CTLA-4:B7 binding by IL-2 generation and cell cycle progression suppression.[24]

Researchers have proposed that CTLA-4 regulation may result in clinically beneficial outcomes in tumour models. T-cells in many human malignancies are not adequately activated against target cells expressing tumor-associated antigens (TAAs). It is generally accepted that when CTLA-4 is present, these TAAs are unable to begin enough activating signals via the B7/CD28 and major histocompatibility complex/T-cell receptor (MHC/TCR) co-stimulatory pathways. T-cells obtained from mice implanted with fibrosarcoma have been shown to lose their ability to produce lymphocytokines over the course of a few weeks.[25-27] CTLA-4 inhibition reverses this by increasing levels of interleukin-2 (IL-2) and interferon-gamma (INF-gamma) production in a tumour stage-dependent manner. In order to determine whether CTLA-4 inhibition may be utilized to treat common human malignancies in pre-clinical animal models, several investigations were carried out.[28]

PROGRAMMED DEATH CELL (PD-1)

The first immunoglobulin G4 (IgG4) PD-1 immune checkpoint inhibitor antibody to be developed for humans is called nivolumab. It prevents the PD-1 receptor from interacting with its ligands, PD-L1 and PD-L2, hence preventing the cellular immune response. Nivolumab, an anti-PD-1 antibody, has received FDA approval for the treatment of melanoma in 2014 and renal cell carcinoma in 2015. It was also approved by the FDA in March 2015 for the treatment of squamous lung cancer, and on October 9, 2015, the FDA expanded the use of nivolumab for metastatic non-small cell lung cancer.[29] A genetically modified anti-PD-1 mAb called nivolumab was created by immunizing transgenic mice for human immunoglobulin loci with PD-1/human IgG1 Fc fusion protein and human PD-1-expressing recombinant Chinese hamster ovary cells. The S228P mutation in the hinge region of nivolumab decreases Fc exchange with serum IgG4 molecules to increase stability and lower therapeutic variability. Nivolumab inhibits PD-1's interactions with both PD-L1 and PD-L2, binds PD-1 with high affinity (KD=2.6 nmol/L by Scatchard analysis to polyclonally activated human T cells), and promotes memory response to tumour antigen-specific T cell proliferation.[30]

The surface receptor PD-1 (CD279) was first found on a murine T cell hybridoma and was presumed to be involved in cell death. However, it has recently been established that PD-1, which is similar to CD28, is predominantly involved in inhibitory immune signalling and is an important regulator of adaptive immune responses.[31] Follicular helper T cells, for example, express PD-1 constitutively in both humans and mice. Although the majority of circulating T cells do not exhibit the receptor, stimulation via the T cell receptor (TCR) complex or exposure to cytokines including IL-2, IL-7, IL-15, IL-21, and transforming growth factor (TGF)- may cause them to activate it. In pathological situations,[32] PD-1 may regulate the functioning of other cell types including mast cells, Langerhans cells, myeloid dendritic cells, B cells, and others. PD-L1 and PD-L2 are the two ligands for PD-1. Both are present on the surface of antigen-presenting cells, including dendritic cells, macrophages, and monocytes, but their expression in different non-lymphoid organs varies.[33] The key factor known to cause the activation of PD-L1 and PD-L2 is interferon-γ. On its intracellular tail, PD-1 has an immunoreceptor tyrosine-based inhibition motif (ITIM) and an immunoreceptor tyrosine-based switch motif (ITSM). Tyrosine residues in these cells get phosphorylated as a result of PD-1 interaction, which sets off an intracellular signalling cascade that mediates the dephosphorylation of TCR proximal signalling components.[34] Recent research has revealed that CD28 is the main target among them. When TCR stimulation is present, CD28 provides vital signals that are crucial for T cell activation. By interfering with early TCR/CD28 signaling and related IL-2-dependent positive tumors, PD-1 signaling reduces cytokine production [such as IL-2, IFN-γ, and tumour necrosis factor (TNF)-α], cell cycle progression, and pro-survival Bcl-xL gene expression, as well as transcription factors implicated in effector functions such as T-bet

and Eomes. As PD-1 signal transduction can only take place during TCR-dependent signaling, it is only significant during simultaneous T-cell activation. It is yet unclear how PD-1 signaling operates in other cell types that express this receptor, such as B lymphocytes. Overall, PD-1 plays a critical role in immune control to prevent immunopathology and in the maintenance of peripheral tolerance. Mice without the receptor appear healthy at first, but as they mature, they acquire autoimmune illnesses such as lupus-like proliferative glomerulonephritis and arthritis, as well as enhanced inflammation following infections. PD-1 locus genetic variations in people increase risk of developing a number of autoimmune disorders.[35]

PROGRAMMED DEATH LIGAND-1 (PDL-1)

PD-1 ligand (PD-L1, also known as CD279 and B7-H1), a 33-kDa type 1 transmembrane glycoprotein with 290 amino acids and IgC domains in its extracellular region, is a member of the B7 class.[36]

PD-L1 is often expressed by macrophages, certain activated T and B cells and some epithelial cells, especially in inflammatory circumstances. Additionally, tumour cells express PD-L1 as a "adaptive immune mechanism" to evade anti-tumor reactions.[37] The production of Th1 cytokines and other chemical factors, interferons, a high concentration of CD8 T cells in the immune system, and particular gene expression traits are all linked to PD-L1. IFN-γ has been shown to increase the expression of PD-L1, which is linked to the progression of the disease, in ovarian cancer cells.

Alternatively, IFN-γ receptor 1 inhibition has been shown to inhibit PD-L1 expression in acute myeloid leukaemia rodent models through the MEK/extracellular signal-regulated kinase (ERK) and MYD88/TRAF6 pathways.[38] IFN-γ triggers the production of protein kinase D isoform 2 (PKD2), which is crucial for the control of PD-L1. The expression of PD-L1 is suppressed by the inhibition of PKD2 activity, which also strengthens the immune response against tumours.[39] The expression of PD-L1 on the surface of tumour cells elevates as a result of NK cells secreting IFN-γ through the Janus kinase (JAK)1, JAK2 and signal transducer and activator of transcription (STAT)1 pathways.[40] Studies on melanoma cells have demonstrated that the JAK1/JAK2-STAT1/STAT2/STAT3-IRF1 pathway, which T cells produce, may control PD-L1 expression. It seems that IFN-γ which is secreted by T and NK cells, stimulates target cells, including tumour cells, to produce PD-L1 on their surface.[41]

PD-L1 binds to its receptors and activates proliferation and survival signalling pathways in cancer cells, acting as a pro-tumorigenic agent. This study added to the evidence that PD-L1 has a role in the development of the tumour in the future.[42]PD-L1 has also been demonstrated to have non-immune proliferative effects on various tumour cell types. For instance, in renal cancer cells, PD-L1 triggered epithelial to mesenchymal transition (EMT) and stem cell-like phenotypes, demonstrating that the presence of the intrinsic pathway of PD-L1 promotes the advancement of kidney cancer.[43]
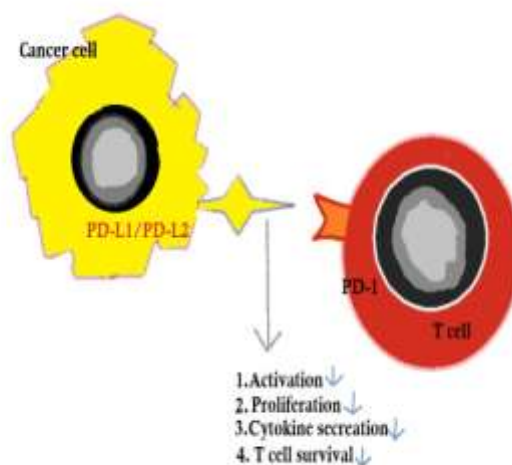

Figure 2: The PD-1/PD-L1 axis inhibits T cell activation, proliferation, and survival and cytotoxic secretion within cancer cell.

FDA Approved Immune checkpoint inhibitors	Molecular Target	Indication
Ipilimumab	CTLA-4	1. Melanoma 2. Melanoma in combination with nivolumab
Nivolumab	PD-1	1. Renal cell carcinoma 2. Hodgkin lymphoma 3. NSCLC 4. Melanoma
Pembrolizumab	PD-1	1. Urothelial carcinoma 2. Hodgkin lymphoma 3. NSCLC 4. Melanoma
Atezolizumab	PD-L1	1. Urothelial carcinoma 2. NSCLC
Durvalumab	PD-L1	1. Urothelial carcinoma
Avelumab	PD-L1	1. Merkel cell carcinoma 2. Urothelial carcinoma

Table 1 : Immune checkpoint inhibitors for cancer immunotherapy approved by FDA

EFFICACY AND MODE OF ACTION OF IMMUNE CHECKPOINT INHIBITORS

When compared to traditional chemotherapies, both CTLA-4 and PD-1 checkpoint inhibitors have improved patient survival in several studies, including those on melanoma, renal cell carcinoma, squamous cell carcinoma, and non-small cell lung cancer. AntiPD-1 therapy was more successful in treating melanoma patients with smaller tumours.[44] In a Phase III clinical trial, a direct comparison of the two checkpoint inhibitors revealed that patients treated with the anti-PD-1 antibody nivolumab had higher response rates (44%) and longer survival times (6.9 months progression-free survival) than patients treated with the anti-CTLA-4 antibody Ipilimumab (19% and 2.8 months, respectively). Nivolumab and Ipilimumab were administered together, and this led to even better response rates (58%) and survival rates (11.5 months).[45]

According to the independent inhibitory actions of CTLA-4 and PD-1 on CD3/CD28-dependent signalling, underlying immunological responses are necessary for checkpoint inhibitor therapy to be effective. Indeed, as it was noted in the preceding section, both PD-1 and CTLA-4 blockades are more efficient in tumours that are immunogenic before therapy or that are infiltrated by T cells or have significant mutation rates.[46]

Type I immune responses, which include IFN- production and cytotoxic T cell activities, are critical for anti-tumor immune responses and have been linked to greater responses to anti-CTLA-4 and anti-PD-1 therapy.[47] Indeed, anti-PD-1 mediated tumour regression has been demonstrated in mice models to need local IFN- γ overexpression. Similarly, IFN-γ and the cytotoxic granule component granzyme B were found to be elevated in regressing melanoma lesions after antiPD-1 treatment. Patients who initially responded to anti-PD-1 therapy but later relapsed revealed tumours with mutations that resulted in a lack of MHC class I surface expression (to prevent cytotoxic T cell recognition) or IFN-response elements.[48]

ADVERSE EVENTS RELATED TO TREATMENT AND THEIR MANAGEMENT

Under physiological circumstances, PD-1 and CTLA-4 suppress autoimmunity and restrict immune activation to prevent bystander injury. Therefore, therapeutic antibody inhibition of these receptors for the treatment of cancer is linked to a variety of adverse events that resemble

autoimmune responses.[49]

Clinical studies that directly examined various immune checkpoint inhibitors and their combinations found that anti-CTLA-4 treatment resulted in higher side effects (27.3%) than anti-PD-1 treatment (16.3%) for patients. When both were used in the treatment, even more patients (55%) were impacted.[50]

Hypophysitis has been documented in roughly 2% to 4% of patients receiving Ipilimumab but in 1% of patients getting PD-1 inhibitors; however, this difference in incidence may not be due to changes in immunological mechanisms of action, but rather to ectopic expression of CTLA-4 in the pituitary gland, resulting to Ipilimumab binding to endocrine cells, followed by complement fixation and inflammation.

Immune checkpoint inhibitors almost commonly cause moderate side effects such diarrhoea, exhaustion, pruritus, rash, nausea, and decreased appetite in their patients. Severe adverse reactions involves severe diarrhea, colitis, increased alanine aminotransferase levels, inflammation pneumonitis, and interstitial nephritis There have also been cases of patients developing type 1 diabetes mellitus or seeing their pre-existing autoimmune disorders like psoriasis go worse. If side effects are particularly severe, treatment may need to stop, albeit the patient may still react later.[51] Surprisingly, certain treatment-related auto-immune reactions, such as rash and vitiligo, have been linked to a better disease prognosis, implying a link between auto-immune and anti-tumor immune responses.[52]

Class of Immune checkpoint inhibitors	Approved agents	Colitis	Rash	Diarrhea	Hypothyroidism	Hypophy
Anti CTLA4	Ipilimumab Tremelimumab	7%-11.6%	12%-68%	31%-49%	4%-4.2%	4%-6%
Anti PD-1	Nivolumab Pembrolizumab	1.3%-2.9%	11.7%-24%	2.9%-11.5%	3.4%-8.5%	0.25%
Anti PD-L1	Atezolizumab Durvalumab Avelumab	0.7%-19.7%	7.4%	11.6%-23%	5.0%-9.6%	0.2%

Table 2: Approved agents and its adverse effects

FUTURE POSSIBILITIES: ENHANCING IMMUNE CHECKPOINT INHIBITORS TREATMENT

PD-1 and CTLA-4 inhibitors are not beneficial in many patients, and even those who respond initially may relapse, emphasising the need for improved or alternative treatments. Alternative inhibitory receptors have been discovered that could possibly be the focus of immunotherapy for the treatment of tumours.[53] These include the TIM-3, LAG-3, TIGIT, and B- and T-Lymphocyte-Associated Protein (BTLA) receptors linked to T cell exhaustion, as well as VISTA, a receptor found on tumor-infiltrating myeloid cells, whose inhibition promoted anti-tumor immune responses in murine models, and CD96, which has been demonstrated to inhibit NK cell activity in murine cancer models.[54]

Immune checkpoint inhibitor combinations with one another or with different therapies are also being investigated. Anti-CTLA-4 and anti-PD-1 therapies worked more well when combined than when administered separately,

although there was a rise in side effects as well.[55] Combining immune checkpoint inhibitors and Indoleamine 2,3 dioxygenase blocking (IDO-blocking) medications has shown encouraging outcomes in mice and is currently undergoing clinical trials in humans. The tryptophan-metabolizing enzyme IDO reduces T cell activity. Macrophages may also hinder the production of therapeutic antibodies or even directly interfere with anti-tumor immunity.[56]

Immune checkpoint inhibitor-based therapy might even benefit from gut microbiota manipulation. The administration of intestinal Bifidobacteria alone was related with decreased tumour growth in a rodent B16 melanoma model by boosting dendritic-cell mediated CD8+ T cell responses.[57] Importantly, giving these microorganisms to the mice increased the therapeutic benefit of the anti-PD-1 medication. In a related study, B. fragilis was administered to sterile mice that had received anti-CTLA-4 treatment, and the tumour growth was inhibited.[58] This effect was most likely achieved by causing a

favourable shift toward Th1 responses. Studies on humans have also demonstrated a positive response to anti-PD-1 therapy in the presence of faecal A. muciniphila, Ruminococcaceae, and Faecalibacterium. Together, these result suggests that human patients may also benefits by managing their gut flora adequately while receiving immune checkpoint inhibitor medication.[59]

As a result, numerous promising novel directions are now being investigated, though ongoing and upcoming clinical trials are still needed to prove their clinical efficacy.[60]

II. CONCLUSION

Although CTLA-4, PD-1 and PD-L1 targeted medicines have been able to extend the average life expectancy of cancer patients, advanced-stage patients still expire at a high rate, emphasising the need for additional advancements in the field. PD-1, PD-L1 and CTLA-4 medicines are seem to be more successful in patients who already possess anti-tumor immunity, which suggests that these medications cannot promote antitumor immune responses in people without such immunity. As we acquire more insight into the mechanisms underlying these medications, however, opportunities are opening up to better utilize them. These include not only focusing on the patients who are most likely to respond through appropriate biomarker screening procedures, but also combining currently prescribed immune checkpoint inhibitors with other complementary medications to help the patients who are unable to respond to the former.

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