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Checkpoint Inhibitors: A novel approach in the avenues for cancer therapy

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Cancer has been on the rise in the Middle East and North African region. There is a need for newer, targeted therapies to combat this trend. Cancer growth and progression are intricately associated with immune suppression and checkpoint inhibitors, that target this immune suppression, presenting a novel treatment avenue. The aim of this review is to summarize the fundamentals and highlight the future of checkpoint inhibitors in cancer therapy. PubMed, SCOPUS and index journals were searched based on key concepts related to checkpoint inhibitors and narrowed down from 2015 to 2021, to present only the most recent and relevant information. The development of immune checkpoint inhibitors is a revolutionary milestone in the field of immuno-oncology. The immune system recognizes and is poised to eliminate cancer but tumors have numerous ways of suppressing the antitumor immune response and upregulation of co-inhibitory receptors, known as immune checkpoints, is a key mechanism in the same. These immune checkpoint pathways normally maintain self-tolerance and limit collateral tissue damage during anti-microbial immune responses but they are used by cancer to evade immune destruction. Drugs interrupting immune checkpoints can thus revive antitumor immune responses by interrupting co-inhibitory signaling pathways and promote immune-mediated elimination of tumor cells. Checkpoint inhibitors are considered to be an effective new addition to the available therapies with a clear role in the first-line treatment of advanced melanoma and in the second-line treatment of advanced squamous non- small cell lung cancers. The review describes the underlying principles of checkpoint blockade, its potential in cancer therapy and the current approved drugs. Combination regimens and recent progress in treatment models have also been briefed in the article. Therapies utilizing checkpoint inhibitors have potent implications in the treatment of specific types of cancers and the continuing research in the field can contribute immensely to better understanding of tumor mechanisms and immunity.

Keywords: Immune Checkpoints, CTLA-4, PD-1, Checkpoint Inhibitors, Immune Therapy, Combination Cancer Therapy

INTRODUCTION

The immune system is a highly regulated entity that is dependent on nuanced stimulatory and inhibitory pathways that ultimately provide effective immunity and maintain tolerance. The growing scientific interests in these mechanisms have led to better understanding of the role of the immune system in tumor growth and progression. One such component that plays a key role is the immune checkpoint, which is taken over by the tumors to evade its eradication. The interplay between the immune checkpoints and tumors is highly complex and researches pertaining to it have led to the development of immunotherapeutic agents that can regulate these compromised checkpoints and provide effective treatment against certain malignancies (Thallinger et al. 2017).

Immune checkpoints: fundamental concepts

Immune checkpoints (ICP) are the body's regulatory mechanisms that play a key role in restraining excessive immune cell mediated damage as well as autoimmune responses. Therefore, they are primarily inhibitory molecules of the immune system. Two such immune checkpoint molecules that have been extensively studied with promising results are cytotoxic T lymphocyte antigen-4 (CTLA-4, also known as CD152) and programmed death-1 (PD-1), also known as CD279 (Figure 1) (Thallinger et al. 2017).

CTLA-4 is an inhibitory receptor found on T cells that binds to its ligands B7-1 (CD80) and B7-2 (CD86) and downregulates the immune response, particularly by attenuating the activation of T cells and promoting T regulatory cells (Torphy et al. 2017; Swart et al. 2016). It

works by counteracting the costimulatory molecule CD28, which also binds to the same ligands. However, CTLA-4 has almost 20 times higher affinity for these ligands and therefore, acts as a negative regulator by being a better competitor than CD28 (Webb et al. 2018). CTLA-4 is also an important factor in self-tolerance, shown by the severe lymphoproliferation in mice with deletion of gene encoding for CTLA-4 (Wei et al. 2018; Postow et al. 2015).

PD-1 is a protein that is expressed on broader categories of cells, such as activated T cells, natural killer (NK) cells, B cells and macrophages (Webb et al. 2018). The ligands of PD-1 are PD-L1 (B7-H1) and PD-L2 (B7-DC) and upon their binding, causes attenuation of T cell activity and suppression of immune responses (Torphy et al. 2017). This is facilitated by the tyrosine phosphatase SHP2 that directly regulates T cell receptor (TCR) signaling. Recently, there has also been evidence that PD-1 preferentially targets CD28 for dephosphorylation compared to TCR. PD-1 is also essential in maintaining peripheral tolerance, evidenced by the development of autoimmune pathologies in mice when there is deletion of the gene encoding for PD-1 ((Wei et al. 2018). These complex regulatory mechanisms and interactions are often exploited by the malignant cells to evade immune destruction and form the basis of immune checkpoint blockade therapies for tumors (Thallinger et al. 2017).

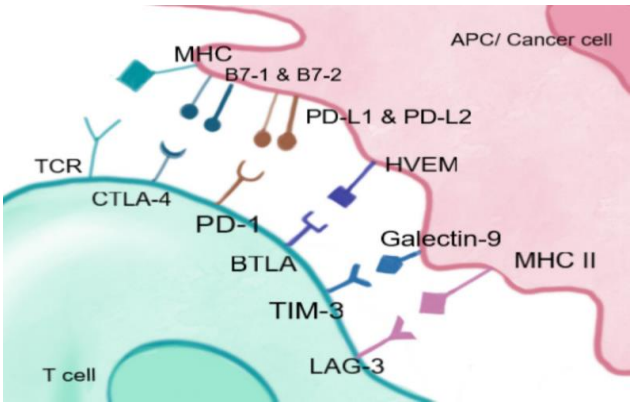

Figure 1: Immune checkpoint receptors and ligands

Immune checkpoint receptors and their known ligands. Some exert inhibitory effects through interaction with more than one ligand, such as TIM-3 and LAG-3. (BTLA, B and T lymphocyte attenuator; LAG-3, lymphocyte activation gene-3; TIM-3, T-cell immunoglobulin and mucin-domain-containing molecule; MHC-II, class II major histocompatibility complex; APCs, antigen-presenting cells; HVEM, herpesvirus entry mediator) (Thallinger et al. 2017).

Role of immune checkpoint blockade in cancer therapies

Established tumors have various mechanisms to suppress antitumor response, such as production of inhibitory cytokines, recruitment of immunosuppressive cells and upregulation of immune checkpoints (La-Beck et al. 2015). Tumors take over the checkpoints, such as CTLA-4 and PD-1, to evade the immune eradication and therapies revolving around these immune checkpoints have shown remarkable clinical responses in certain subsets of patients and have led to the development of immune checkpoint inhibitors as a novel class of immunotherapy, first approved in 2011 (Patel & Minn, 2018; Sharpe, 2017).

CTLA-4 and PD1 are two immune checkpoints that have been extensively studied and consequently there is better understanding of the mechanisms underlying the blockade therapies utilizing these immune checkpoints, particularly CTLA-4 (Patel & Minn, 2018; Sharpe, 2017).

CTLA-4 blockade therapy promotes anti-tumor response in a variety of ways, particularly by facilitating enhanced CD28 mediated positive co-stimulation by blocking the CTLA-4 competition for the common ligands B7-1 and B7-2. However, B7 ligands are not expressed by tumor cells and necessitates tumor cell antigens, which are produced upon the cell death, to be presented by antigen presenting cells (APCs) in order to prime the T-cells. Understanding this priming and the ensuing regulation will potentially help in the development of therapies that can target tumors sensitive to CTLA-4 blockade (Wei et al. 2018).

Studies also suggest that anti-CTLA-4 leads to expansion of tumor neoantigen–specific CD8 T cells within the tumor microenvironment and specific types of CD4 effector T cells rather than a generalized effect on the T cells, which may allude to the possibility that anti-CTLA-4 affects T cell differentiation (Wei et al. 2018).

Depletion of the T-regulatory cell population was also identified in murine-tumor models subjected to anti-CTLA-4 treatment, and this mechanism may also influence the anti-tumor response. Another pathway that contributes to the antitumor response, mediated by anti-CTLA-4, is T cell receptor (TCR) regulation, specifically, by lowering the threshold required for TCR ligation and subsequent T cell activation. This enables even low signal strength antigens to mount an effective T cell response as well as boost the effect of high affinity tumor reactive T cells (Wei et al. 2018). All of these distinct mechanisms brought about by the CTLA-4 blockade, interact and result in better activation of tumor reactive T cells and effective anti-tumor response (Akinleye & Rasool, 2019)

In contrast, PD-1 blockade leads to tumor rejection by replenishing the exhausted T cells. The PD-1 and PD-L1 axes attenuates immune response by affecting the T cell migration, proliferation, and signaling. The PD-1 and PD-L1 blockade therapy, therefore, allows T cells to overcome the suppression and continually work within the tumor microenvironment in the long term (Akinleye & Rasool, 2019)

Specific immune checkpoint inhibitors

The 7 immune checkpoint inhibitors approved by the US Food and Drug Administration (FDA) include anti

CTLA-4 antibodies (Ipilimumab), anti PD-1 antibodies (Pembrolizumab, Nivolumab and Cemiplimab) and anti PD-L1 antibodies (Atezolizumab, Avelumab and Durvalumab), which are briefly discussed below.

Ipilimumab

Ipilimumab was the 1st active immunotherapy that gained FDA approval for unresectable or metastatic melanoma based on a randomized double-blind phase III study. It is a human immunoglobulin IgG1 monoclonal antibody that targets the CTLA-4 coinhibitory receptor. Ipilimumab binding to CTLA-4 prevents the T cell receptors from interacting with CD80/CD86 on antigen presenting cells (APCs); thus, allowing CD80/CD86 to interact with costimulatory receptors to promote immune activation. Ipilimumab is administered intravenously (IV) at 3 mg/kg over 90 minutes every 3 weeks for 4 total doses (Pennock & Chow, 2015; Martins et al. 2019). The drug has exhibited delayed onset of anticancer therapy. Side effects mainly occurred during the 3rd or 4th dose and they include fatigue, diarrhea, pruritus, rash and colitis (Martins et al. 2019).

Pembrolizumab

Pembrolizumab, a humanized IgG4-κ monoclonal antibody targeting PD-1 receptor on T cells, was first approved for the treatment of advanced melanoma (after failure of ipilimumab and if positive for BRAF V600 mutation, failed BRAF inhibitor therapy) (Vaddepally et al. 2020; Centanni et al. 2019). Pembrolizumab binding to PD-1 prevents this receptor from interacting with the tumor cell ligands (which nullifies signals that would otherwise cause inhibition of T cell proliferation and cytokine production), thus promoting immune activation. Pembrolizumab has been recently approved for non-small cell lung cancer (NSCLC), Hodgkin's lymphoma, urothelial carcinoma and gastric cancer as well (Centanni et al. 2019). It is given IV at 2mg/ kg over 30 minutes every 3 weeks until disease progression/ severe toxicity. The most common adverse effects include fatigue, pruritus, nausea, skin rash, diarrhea and vitiligo (La-Beck et al. 2015).

Nivolumab

Nivolumab is another human IgG4-κ monoclonal antibody targeting PD-1 receptor on T cells which was initially approved for the treatments of advanced/ unresectable/ metastatic melanoma, NSCLC and metastatic squamous and non-squamous cell lung cancer. Subsequently it has also been approved for renal cell carcinoma, Hodgkin lymphoma, squamous cell cancer of the head and neck (SCCHN), urothelial carcinoma, colorectal cancer and hepatocellular carcinoma as well (Vaddepally et al. 2020; Centanni et al. 2019). Clinical trials that have been conducted support the safety of using Nivolumab in those who were previously treated with Ipilimumab. The drug is given IV at 3mg/kg over 60 minutes every 2 weeks until disease progression or unacceptable toxicity. The common side effects include fatigue, pruritus and nausea (La-Beck et al. 2015).

Cemiplimab

Cemiplimab is a human monoclonal antibody against PD-1 receptor on T cells and blocks its interaction with ligands PD-L1 and PD-L2. It was approved to treat locally advanced or metastatic cutaneous squamous cell carcinoma in patients who are not candidates for curative surgery or radiotherapy (Vaddepally et al. 2020). The phase II trial of the drug produced clinically significant responses against the tumors, when given as 3mg/kg IV once every 2 weeks (or 350 mg once every 3 weeks). Cemiplimab has an acceptable safety and tolerability profile. The adverse effects were manageable with appropriate treatment or discontinuation of the drug (Lee et al. 2020).

Atezolizumab

Atezolizumab is a fully humanized IgG1 monoclonal antibody (mAb) that binds to PD-L1. It works by blocking the PD-L1 from interacting with both PD-1 and B7-1. It is a recently approved drug for the treatment of NSCLC and urothelial carcinoma (Centanni et al. 2019). It is administered as 1200 mg dose every 3 weeks, initially as a 60-min intravenous infusion, and then adjusted accordingly. The most common adverse effects were fatigue, decreased appetite, nausea, pyrexia, diarrhea, rash, pruritus, arthralgia, and headache (Akinleye & Rasool, 2019).

Avelumab

Avelumab is a human IgG1 mAb targeting PD-L1. This also falls under the category of drugs which were recently approved and is being utilized for the treatment of Merkel cell and urothelial carcinoma (Akinleye & Rasool, 2019; Vaddepally et al. 2020). The recommended dose is 10 mg/kg, administered every 3 weeks as a 60-min intravenous infusion. The common treatment-related adverse events are fatigue, influenza-like symptoms, fever and chills (Akinleye & Rasool, 2019).

Durvalumab

Durvalumab is a human IgG1 mAb against PD-L1. This was also newly approved as a second-line therapy for the treatment of NSCLC and urothelial carcinoma. Durvalumab is administered every 2 weeks as a 60-min intravenous infusion at doses of 10 mg/kg (Centanni et al. 2019).

These immune checkpoint inhibitors have shown a drastic improvement, with acceptable toxicity profile, in the overall survival of patients afflicted with cancer. In addition to these drugs, a few other novel checkpoint inhibitors, such as CK-301, BMS-936559, CS-1001, are currently undergoing different phases of trials and may prove to be of use in the future (Akinleye & Rasool, 2019).

Combination therapies

Since acceptable success was achieved during the laboratory and clinical phases of immune checkpoint inhibitor monotherapies, it stands to reason that the next step is the combination of the drugs, so as to improve the therapeutic reach to more tumor populations.

Studies and trials have indeed pointed to the feasibility of this combination approach which have led to selected combination regimens for specific tumor types. Combination therapy with Ipilimumab and Nivolumab is used in the treatment of unresectable or metastatic melanoma, certain classifications of renal cell carcinoma and patients with mismatch repair deficient (dMMR) metastatic colorectal cancer, with appropriate indications (Vaddepally et al. 2020).

However, the exact mechanisms that underlie these improved anti-tumor responses, when multi-drug regimens are implemented, are still under investigation. Both CTLA-4 and PD-1 attenuate T cell activity through distinct mechanisms involving molecules that exert effects on different cell populations. Therefore, concurrent blockade of both checkpoints may involve multiple mechanisms that ultimately lead to better therapeutic response. Whether this is due to the individual pathways, unique to each checkpoint inhibitor, causing an additive effect or a separate repertoire of pathways, is a subject of interest that can further the treatment options available (Centanni et al. 2019). Challenges still remain, however, as to the delineation and identification of responders and non-responders and adapting the therapeutic regimen accordingly, as well as methods to tackle the increased incidence and severity of immune related adverse events (Jenkins et al. 2018; Darvin et al. 2018).

ICP inhibitors and immune related adverse events

While ICP inhibitors have markedly changed the landscape of immune-oncology, the results have not been without caveats. The primary mechanisms of checkpoint inhibitors, such as reducing T-cell tolerance and subsequent activation of T-cells, have led to the development of various immune related adverse events (irAEs) during the course of treatments (Bajwa et al. 2019). Increased levels of pre-existing antibodies, inflammatory cytokines and cross reactivity of T cells between cancerous and normal cells due to the blockade of immune checkpoints, disrupt the immune homeostasis and result in patients developing irAEs with symptoms similar to those observed among autoimmune diseases (Choi & Lee, 2020).

These immune related adverse events span many organ systems and common side effects include gastrointestinal, dermatologic, endocrine systems. Generally, anti CTLA-4 agents show increased incidence and severity of gastrointestinal side effects than by PD-1/PD-L1 inhibitors (Choi & Lee, 2020). Clinical trials involving anti CTLA-4 drug Ipilimumab have shown that irAEs of grade 3 and above are more prevalent in the subset of patients who received high dose 10mg/kg Ipilimumab, compared to those who received 3mg/kg dose, suggesting a dose-dependent risk. Studies have also been able to associate a higher risk of irAEs with longer duration of treatment (Martins et al. 2019).

On the other hand, irAEs related to anti- PD-1 antibodies occur less often, usually within the first 6 months of staring the regimen. The relatively less irAEs than CTLA-4 blockers are because PD-1 and PD-L1 govern immune resistance further down the inflammatory cascade ((Martins et al. 2019; Centanni et al. 2019). They also affect endocrine organs more frequently, namely the thyroid, as opposed to anti CTLA-4 antibodies (Martins et al. 2019).

While ICIs have the potential to cause toxicities involving various organ systems, the risk of fatal adverse events is in fact lower than the conventional treatments, with the incidence ranging between 0.3% and 1.3%. It is necessary to manage these with a multidisciplinary approach so as to enable accurate assessment, early recognition and individualised monitoring strategies and reap better outcomes (Martins et al. 2019; Bajwa et al. 2019).

Future avenues for ICP inhibitors

The growing interest in immune checkpoints and their inhibitors, owing to the favorable outcomes in antitumor studies, have led to discovery of new immune checkpoints in recent years, such as B and T lymphocyte attenuator (BTLA- an immunoglobulin), Programmed Death-1 homolog (PD-1H- cell surface molecule), T-cell immunoglobulin and mucin-domain-containing molecule (TIM-3- Th1 specific cell surface protein) and Poliovirus receptor (PVR)-like proteins (Torphy et al. 2017; Bajwa et al. 2019). These newly emerging immune checkpoints may be used in combination with other immune therapies to help intensify the immune response. However, their implementation depends on the success of the ongoing preclinical trials.

The emergence of checkpoint blockade as potential cancer therapy has also raised the possibility of combination cytotoxic and immunotherapeutic regimens as one of the many approaches towards tumor eradication, such as combination chemotherapy or radiotherapy (Bajwa et al. 2019).

Checkpoint Blockade and Chemotherapy

Chronic pro-cancer inflammation mediated by intrinsic and extrinsic cell pathways such as vascular proliferation has prevented total tumor eradication by chemotherapy. Immune checkpoint blockade provides an opportunity to change the inflammatory tumor microenvironment by utilizing active tumor-specific CD4+ and CD8+ T-cells and converting tumor-associated inflammation to an anti-cancer state (Thallinger et al. 2017).

Clinical studies in metastatic melanoma have shown improved disease control with combination Ipilimumab and

chemotherapy and have shown good results even in cases of brain metastasis. Similar benefits have been observed in small cell lung cancer (SCLC) and NSCLC as well (Swart et al. 2016; Pennock et al. 2015; Bajwa et al. 2019).

Checkpoint Inhibitors and Radiation Therapy

Radiation therapy may initiate an inflammatory response that encourages tumor expression of inhibitory ligands which can subsequently be blocked by checkpoint blockade. Furthermore, radiation causes local tumor destruction, increased immune activity, and an abscopal effect- wherein there is shrinkage of tumors elsewhere in the body, in addition to the local site of irradiation (Thallinger et al. 2017; Swart et al. 2016).

Favorable outcomes in preclinical studies in radiation therapy and CTLA-4 inhibition have also instigated many clinical trials. For these reasons, immune checkpoint inhibitors and radiotherapy are promising components of anti-cancer combination therapy.

Checkpoint Blockade and Bacterial Vaccination Vectors

Attenuated strains of *Listeria monocytogenes* have been developed with deletion of the internalin B and actin A genes, which can express tumor-associated antigens. These strains have been used as tumor vaccination vectors and appear to elicit tumor-specific Th1 CD8+ immune responses in murine breast cancer. Since the anti-tumor effects mediated by *Listeria* vaccines are largely CD8+ mediated, there may be a potential avenue for combination *Listeria* and anti-CTLA-4 therapy, as CTLA-4 is expressed on effector T-cells. Combination of immune checkpoint blockade and bacterial tumor vaccine therapy is an encouraging future prospective that is worth exploring in murine cancer models (Patel, 2015; Marin-Acevedo et al. 2018).

Checkpoint Blockade and DNA Methyltransferase Inhibitors

Solid tumors are usually unresponsive to immunotherapy but recent studies suggest that epigenetic modifying drugs can help in forming antitumor immunity. DNA methyltransferase inhibitors (DNMTi) have shown to increase tumor immunogenicity by upregulating class I major histocompatibility complex (MHC I), as well as increasing antigen presentation, particularly cancer- testis antigens. They have also demonstrated the stimulation of natural killer cell and CD8 T cell mediated cytotoxicity by enhancing the expression of chemokines and activating the associated ligands on the surface of tumor cells. Their ability to regulate adaptive and innate immune responses has established the reduction of tumor associated immunosuppression. Addition of PD-1/ PD-L1 and CTLA-4 checkpoint inhibitors to the regimen augments the response to DNMTi and leads to improved overall therapeutic effect (Saleh et al. 2015). Currently, two DNMTi have been approved by the US Food and Drug Administration (FDA)- Azacitidine and Decitabine. Various phase I clinical trials are, at present, assessing the efficacy of this combination immunotherapy.

Checkpoint inhibitors and BRAF inhibitors

BRAF is a human gene that encodes for a proto-oncogene known as B-Raf. Evidence shows that inhibition of the BRAF pathway has a profound effect on antitumor immunity through multiple mechanisms, including effects on dendritic cell function and natural killer cell activation. However, resistance to this blockade has also been noted through expression of immunomodulatory molecules within tumor microenvironment and presence of stromal mediated immunosuppression (Reddy et al. 2016). Nevertheless, the overall favorable immune effects of BRAF blockade provides a sound rationale for developing combination therapies with checkpoint inhibitors such as PD-1/ PD-L1 inhibitors. Pre-clinical data and ongoing clinical trials reflect promising results, but concerns still remain regarding the toxicity profiles and adverse events following combination regimens. Current trials highlight the need for a personalized approach for optimal results that can improve therapeutic responses whilst reducing resistance to therapy.

CONCLUSION

As one the leading causes of morbidity and mortality, tumors and antitumor regimens have long been the subjects of various researches, which have only led to better and wider range of available therapies. Immune checkpoint inhibitors are one such exciting treatment modality that has shown dramatic results in related studies. Researches are also being aimed at deepening our understanding of different aspects of tumor microenvironment and host characteristics that may be conferring resistance to immune checkpoint blockades or limiting the antitumor responses. Trials, studying these checkpoint inhibitors' role in combination with other anticancer regimens, are also being undertaken and this has the potential to revolutionize the field of anticancer research.

CONFLICT OF INTEREST

The authors declared that present study was performed in absence of any conflict of interest.

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AUTHOR CONTRIBUTIONS

Vaishnavi Bose, Shriya Devendra Tayade, Ashna Ameer, Pooja Mahesh Sikotra, Godfred A. Menezes.

VB, SDT, AA & PMS searched and collected data, carried

out critical review and drafted the initial manuscript. VB & GAM did the final revision and drafting. All authors have read and approved the final manuscript.

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