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Immune Checkpoint Inhibitors: New Horizon in the Management of Cancer

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ABSTRACT

Cancer immunotherapy is the new light of hope and life among cancer patients. Immune checkpoint inhibitors have offered major advances in the care of individuals with a variety of advanced solid tumors. The immune system recognizes and is poised to eliminate cancer, but is held in check by inhibitory receptors and ligands. The immune checkpoint pathways maintain self-tolerance and limit the collateral tissue damage. But which is then taking over by cancer to evade immune destruction. Drugs inhibiting immune checkpoint inhibitors are developed and was belongs to the classes namely antiCTLA-4, anti-PD-1, and anti-PD-L2. Immunotherapy makes the body fight against cancer with the immune system itself.

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INTRODUCTION

The conventional anticancer treatment strategies include surgery, chemotherapy, and radiotherapy [1, 2]. Though many of these therapies have offered considerable benefit in the management of primary tumors, the existence of disease relapse has still encountered the problem that results from residual malignant cells an tumor metastases [3, 4]. Cancer immunotherapy is becoming a most promising and powerful strategy among different treatment options which was proved against malignancies [3, 5-8]. Cancer can be defeated by utilizes the body's immune system to induce anti-tumor responses [3, 5-8]. In the newly developing world, the researchers paved the way for the emergence of new kind of therapy in the management of cancer, Immune checkpoint inhibitors.

Our goal in this article is to summarize the fundamental molecular mechanism in immune checkpoint blockade. Indications and side effects of the various checkpoint inhibitors along with the management of the side effects have been discussed. Developing strategies in the management of cancer also mentioned. We hope that this review will be of interests to the clinical pharmacists and the medical professionals.

NEW TRENDS IN CANCER THERAPY

At present, new strategies aimed to block of immune checkpoint regulators, overcome immune tolerance through engineered T cell therapy, by the identification of novel tumor antigens through next-generation sequencing opened a new era of cancer immunotherapy [10-12]. Cancer immunotherapy can be passive or active immunotherapy [13, 14]. Passive immunotherapy is the administration of agents such as mAbs, lymphocytes or cytokines that enhance existing anti-tumor response [9]; active immunotherapy attempts to stimulate self-immune system to attack tumor cells via vaccination, non-specific immune modulation, or targeting specific antigen receptors [9].

IMMUNE CHECKPOINT INHIBITORS

Immune checkpoint inhibitors are a class of drugs that increases the immune response against cancer cells [15-17]. The immune system consists of various checkpoint pathways which focusing on T-cell activation. [18]. Molecules that play a crucial role in checkpoint regulation are T-cell surface molecules CTLA-4, PD-1, T-cell immunoglobulin, and mucin domain-containing protein 3 (Tim-3), and lymphocyte activation gene-3(LAG-3) [24]. Tumor

expressions of these markers will result in under activity or even depletion of the immune system [19]. So that, these molecules are highly attractive as targets for removing the inhibition and allow cytotoxic T cells to attack cancer cell for destruction [9, 26]. In 2011, FDA approved anti-CTLA-4 antibodies ipilimumab for the treatment of metastatic melanoma, which marked the beginning of a new era for cancer immunotherapy [20, 25]. Subsequently, antibodies against PD-1 pembrolizumab and nivolumab have been approved in 2014, also for the metastatic melanoma [21]. Nivolumab has also been approved in 2015 for previously treated advanced or metastatic squamous lung cancer, an approval later expanded also too small cell lung cancer [22]. In 2016, anti-PD-L1 atezolizumab was approved for bladder cancer [24] and nivolumab was approved for Hodgkin lymphoma [23] (Table 1).

MECHANISM THAT DESCRIBES THE ACTIONS OF IMMUNE CHECKPOINT INHIBITORS

A. MECHANISMS OF ACTION OF CTLA 4 BLOCKADE

The primary mechanism involved in the CTLA4 blockade is by direct blockade of CTLA4 competition for B7-1 and B7-2 costimulatory ligands which resulting in unrestrained CD28-mediated positive costimulation. Indeed, crystallographic structural analyses of the ipilimumab: CTLA4 complex reveals that the ipilimumab binding epitope overlaps with the B7 interaction domain, that leads to steric inhibition of B7 interactions[27]. Considering the facts of effective antigen presentation, CTLA4 blockade then augments CD28 costimulation and thus activation. Emerging evidence indicates that anti-CTLA4 does not shows a generalized effect on all T cells. CTLA4 inhibition leads to specific expansion of tumor neoantigen–specific CD8 T cells within the tumor microenvironment, but not secondary lymphoid organs [28]. Consistent with this notion, antiCTLA4 leads to expansion of specific tumor-infiltrating T-cell populations including a subset of phenotypically exhausted CD8 T cells and a PD-1+ICOS+TBET+ Th1-like CD4 effectors T-cell population [29]. Again, the expansion of specific types of CD4 effectors T cells gives the possibility that anti-CTLA4 not only amplify T-cell activation but can also affect T-cell differentiation. The extent to which effects on T-cell lineage choices may contribute to the mechanisms and efficacy of immune checkpoint blockade therapies remains unclear. CTLA4 blockade intensifies antitumor immunity through modulation and expansion of particular T-cell populations. Tremelimumab is a fully human IgG2 antibody and ipilimumab is a fully human IgG1 antibody, which is notable because IgG1 antibodies more effectively mediate antibody-dependent cell-mediated

toxicity (ADCC) than IgG2 antibodies depending on their respective binding affinity for human Fc receptors [30]. The pooled data from phase 1 and phase 2 trials support that anti-CTLA4 both enhances cell-intrinsic effector function through the blockade and induces Fc-mediated cellular depletion. Modulation of the TCR repertoire also considered for therapeutic effects of the CTLA4 blockade. CTLA4 blockade primarily produces changes in genes associated with proliferation and cell cycle.

B.MECHANISMS OF ACTION OF PD-1 BLOCKADE

PD-1 blockade can produce tumor rejection through rejuvenation of CD8 T cells that leads to increased functional activity and frequency. In spite of continued PD-L1 expression within the tumor microenvironment, depleted T cells are begun to rejuvenate and induce an effective immune response. Recent evidence reports that a subset of CXCR5+ PD-1+ CD8 T cells accountable for expeditious proliferative development following PD-1 blockade [31]. Recent data from a neoadjuvant trial of nivolumab in the context of non–small cell lung cancer reveals that anti– PD-1 therapy enhances neoantigen-specific T-cell responses [32]. There exists a high degree of phenotypic and functional heterogeneity within depleted CD8 T cells [33]. CD4 helper T cells may also strengthen antitumor immunity by increasing CD8 T-cell and antibody entry into peripheral tissue sites. [34,35]. Blockade of the PD-1 signaling axis restores T-cell activity through modulation of TCR signaling and gene expression and also reverse the associated metabolic reprogramming to an extent, which in part directs the T-cell restoration [36]. Antibodies targeting PD-L1 are more enough to induce immune tumor rejection through fading of CD8 T-cell cytotoxicity. How these apparently disparate findings can be integrated remains to be fully understood. Nonetheless, they raise the possibility that PD-L1 can inhibit T cell-mediated tumor cell killing through both cell-autonomous and no autonomous mechanisms.

ADVERSE DRUG REACTIONS AND SIDE EFFECT PROFILE OF IMMUNE CHECKPOINT INHIBITORS

Dermatological effects include rash and mucosal irritation. Rashes associated with checkpoint blockade often appear as faintly erythematous, reticular, and maculopapular particularly at extremities of the trunk. The most common side effect reported with Ipilimumab was rashes while with the use of PD-1 inhibitors it was reported to occur oral mucositis and dry mouth.

Gastrointestinal side effects include diarrhea and colitis, of which diarrhea is common in patients who have been treated with checkpoint-blocking antibodies. Comparing the incidence, there is a much higher incidence of diarrhea in patients receiving CTLA-4 blocking antibodies than those targeting PD-1/PDL1. Distinguishing diarrhea (increase in the frequency of stool) from colitis (abdominal pain, radiographic or endoscopic findings of colonic inflammation) is important.

HEPATOTOXICITY

Hepatitis is being determined by elevations in aspartate aminotransferase (AST), aminotransferase (ALT) levels and to a lesser extent total bilirubin. Although most episodes present only as asymptomatic laboratory abnormalities, some patients have an associated fever.

ENDOCRINOPATHY

Immune-related adverse events that affect the pituitary, adrenal, and thyroid glands often manifested with nonspecific symptoms such as nausea, headache, and fatigue. Hypothyroidism is more frequently reported than hyperthyroidism and if patients are evaluated for fatigue that possibly results of endocrinopathy, it is important to distinguish primary hypothyroidism (low free T4 and high TSH) from hypophysitis, which leads to secondary hypothyroidism (low free T4 and low TSH). The most emergent endocrinopathy is an adrenal crisis associated with dehydration, hypotension, and electrolyte imbalances such as hyperkalemia and hyponatremia.

Several pulmonary inflammatory conditions have reported in patients receiving ipilimumab, including sarcoidosis and organizing inflammatory pneumonia. In patients treated with PD-1 blocking agents pneumonitis is being reported.

Inflammation of components of the eye has been evidenced with the CTLA-4 blockade. The conditions include episcleritis, conjunctivitis, and uveitis which are presented with symptoms such as photophobia, pain, dryness of the eyes, and blurry vision.

Considering the fact about renal function, the renal insufficiency developed in patients who are treated with Ipilimumab was thought to be due to the drug. Histopathology analyses of

kidney biopsies showed the pathology of acute granulomatous interstitial nephritis and lupus membranous nephropathy.

Neurologic syndromes are being associated with checkpoint blockade with ipilimumab which includes posterior reversible encephalopathy syndrome, aseptic meningitis, enteric neuropathy, and transverse myelitis. Hematologic Syndromes consisting of Red cell aplasia, neutropenia, and acquired hemophilia A55 also have been described in patients treated with ipilimumab, as has thrombocytopenia.

MANAGEMENT OF SIDE EFFECTS

DERMATOLOGICAL SYMPTOMS

Topical corticosteroid creams can be used to treat rashes. Oral antipruritics such as hydroxyzine HCl or diphenhydramine HCl can be beneficial in problematic pruritis. Severe rashes (grade3andabove) should be managed with oral corticosteroids. For rarely reported cases of Stevens-Johnson syndrome and toxic epidermal necrolysis go for permanent discontinuation of checkpoint blockade and require hospitalization for intravenous corticosteroids, dermatologic evaluation, and fluid/electrolyte management. Oral corticosteroid rinses or lidocaine can treat the symptoms of oral mucositis.

Diarrhea:-Patients should maintain oral hydration. Antimotility agents like oral diphenoxylate HCl and atropine sulfate 4 times a day can be helpful. If symptoms persist for more than 3 days or increase, intravenous corticosteroids (up to 2 mg/kg methylprednisolone twice a day) can be opted.

ENDOCRINOPATHIES

When hypophysitis is suspected course of high-dose corticosteroids (1 mg/kg of prednisone daily) given during the acute phase can reverse the inflammatory process. Secondary hypothyroidism is treated with levothyroxine and secondary hypoadrenalism treated with replacement doses of hydrocortisone, typically 20mg each morning and 10mg each evening. In adrenal crisis, intravenous corticosteroids and immediate hospitalization are required. Consultation with an endocrinologist, aggressive hydration, and evaluation for sepsis is critical in the management of suspected toxicities. Management of hypothyroidism involves replacement with thyroid hormone (levothyroxine).

For pulmonary symptoms, treatment should consist of high doses of corticosteroids such as 2mg/kg of intravenous methylprednisone. Additional immune suppression with infliximab, mycophenolate mofetil, or cyclophosphamide is advised.

For eye-related symptoms consultation with ophthalmologists recommended, and treatment with a topical intraocular corticosteroid such as 1% prednisolone acetate suspension may beneficial.

Corticosteroids are not indicated in patients with asymptomatic elevations in amylase/lipase without other symptoms of pancreatitis.

SAFETY AND EFFECTIVENESS

By 2015, pooled data from clinical trials confirm that approximately 20% of patients have long-term survival of at least 3 years after Ipilimumab therapy. Nivolumab has clinically meaningful activity and a manageable safety profile in previously treated patients with advanced, refractory, squamous non-small cell lung cancer. These data support the assessment of nivolumab in randomized, controlled, phase 3 studies of first-line and second-line treatment. Nivolumab and Pembrolizumab demonstrated highly durable response rate with minimal toxicity in a large phase1 studies involving patients with advanced melanoma. Atezolizumab is the first checkpoint inhibitor to provide an overall survival benefit in a patient population with low or non-detectable levels of PD-L1 expression and never smokers in non-small cell lung cancer and also showed durable activity and good tolerability. Duralumin exhibits attainable safety profile and significant clinical activity in patients with Urothelial Bladder Cancer [39].

FUTURE ADVANCES IN THE FIELD OF CANCER THERAPY

Research led by Melbourne scientists discovered a new type of anti-cancer drug that can put cancer cells into permanent sleep, without the harmful side effects caused by conventional cancer therapies. They investigated that KAT6A and KAT6B inhibition and their benefits in the treatment of cancer. The compounds had shown promising effects in preclinical testings. Researchers at The University of Texas at Austin developed a new approach to treating cancer by using enzyme therapy in which immune system boosted by this enzymes and fight back. This is the first time one has designed to take on the role of immune checkpoint

inhibitor. PEG-KYN designed to degrade kynurenine, which blocks immune cells that impedes normal surveillance.

SUMMARY

We can summarize that the recent advances of cancer immunotherapy really a boon to cancer patients. Apart from the conventional treatment options now the patients have more options to improve their health which includes cancer vaccines, CAR-T cell and checkpoint inhibitors. Nowadays the immune checkpoint inhibitors are most effective in the fight against the tumor cells and there is evidence for their effectiveness. Combination therapy, particularly personalized combination therapies that specifically drive each patient' cancer biology via new techniques might be an optimistic treatment strategy to treat cancer in the future. There exist some kind of side effects with the immune checkpoint inhibition, identification, and management of them is of prime importance as a key factor for treatment success.

Table 1. Summary of the tumor types for which immune checkpoint blockade therapies are FDA-approved [37].

Indication	Therapeutic agent	FDA approval year
Melanoma	Ipilimumab	2011
Melanoma	Nivolumab	2014
Melanoma	Pembrolizumab	2014
Non–small cell lung cancer	Nivolumab	2015
Non–small cell lung cancer	Pembrolizumab	2015
Melanoma (BRAF wild-type)	Ipilimumab + nivolumab	2015
Melanoma (adjuvant)	Ipilimumab	2015
Renal cell carcinoma	Nivolumab	2015
Hodgkin lymphoma	Nivolumab	2016
Urothelial carcinoma	Atezolizumab	2016
Head and neck squamous cell carcinoma	Nivolumab	2016
Head and neck squamous cell carcinoma	Pembrolizumab	2016
Melanoma (any BRAF status)	Ipilimumab + nivolumab	2016
Non–small cell lung cancer	Atezolizumab	2016
Hodgkin lymphoma	Pembrolizumab	2017
Merkel cell carcinoma	Avelumab	2017
Urothelial carcinoma	Avelumab	2017
Urothelial carcinoma	Durvalumab	2017
Urothelial carcinoma	Nivolumab	2017
Urothelial carcinoma	Pembrolizumab	2017
MSI-high, MMR-deficient metastatic colorectal cancer	Nivolumab	2017
Pediatric melanoma	Ipilimumab	2017
Hepatocellular carcinoma	Nivolumab	2017
Gastric and gastroesophageal carcinoma	Pembrolizumab	2017
Non–small cell lung cancer	Duralumin	2018
Renal cell carcinoma	Ipilimumab + nivolumab	2018

NOTE: A summary of the tumor indications, therapeutic agents, and year of FDA approval for immune checkpoint blockade therapies. FDA approval includes regular approval and accelerated approval granted as of May 2018. Ipilimumab is an anti-CTLA4 antibody. Nivolumab and pembrolizumab are anti–PD-1 antibodies. Atezolizumab, Wavelab, and duralumin are anti–PD-L1 antibodies. Tumor type reflects the indications for which treatment have been approved. Only the first FDA approval granted for each broad tissue type or

indication for each therapeutic agent is noted. In cases where multiple therapies received approval for the same tumor type in the same year, agents are listed alphabetically. Abbreviations: MSI, microsatellite instability; MMR, mismatch repair.

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