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Review Article

Mechanistic basis for Cancer Immune Evasion and role of immune checkpoint blockades in Immuno-Oncology

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Abstract

Cancer biology clinical breakthroughs in this millennium requires the development of new methods and techniques to suit the challenge of the global health menace. Immunotherapy is a technique that has engendered advancement in cancer studies. Immuno-oncology aims at the recognition of tumour antigens and elimination of tumour cells. In this paper, the pathogenesis of carcinogenesis and role of immunosurveillance in tumour prevention is critically analyzed. The paper also attempts to show the role of MHC-I and IFN signaling, the concerted effort of Cytotoxic T-Lymphocyte-Associated Protein 4 (CTLA-4), Programmed Cell Death Protein 1 (PD-1) and Programmed Death-Ligand 1 (PD-L1), and metabolic alteration in immune evasion mechanism of cancerous cells. The use of Immune Checkpoint Inhibitors (ICPIs) in combination with anti-CTLA-4 and anti-PD-1 antibodies has increased survival in some cancers and shows promise in others. When these agents are administered, however, there are toxicities known as "Immune-related adverse events." A brief overview on the dermatologic toxicity, endocrinopathy, hepatotoxicity and diarrhoea/enterocolitis is discussed. This paper concludes by mentioning the promising potential of genomic sequencing technology in cancer immunotherapy.

Introduction

Approximately 19.3 million new cases of cancer and 10.0 million deaths from cancer were registered worldwide in 2020. According to WHO [1], cancer is the sixth leading cause of death globally. GLOBACAN [2] predicts that in 2040, new cases if cancers would have risen to 28.4 million. Cancer cell development is a multifaceted process that involves genetic mutation of normal cells and physiological changes that affect the body's defence mechanism [3]. The transformation of normal cells into cancerous cells necessitates the sequential acquisition of mutations resulting from genome damage caused by DNA replication errors, chemical instability of DNA bases, or attack by oxidative species and other free radicals generated during metabolic processes [4].

Cancer cells have different strategies in escaping destruction, and these are captured in its hallmarks [5]. The ability to evade immune suppression is one of cancer's hallmarks. Tumor cell transformation triggers innate and adaptive immune responses, which aid in the elimination and control of cancer's early stages [6]. The cancer immuno-surveillance or immune-editing mechanism allows the immune system to recognize and kill nascent cancer cells [7]. Through immuno-surveillance, immune cells can inhibit tumour growth through malignant cells recognition and rejection [8]. Studies associated with this have led to discovering novel immunotherapeutic approaches towards cancer [9-11].

In recent times, immune checkpoint inhibitors (ICPIs) have changed the view of oncotherapeutics. Spain, et al. [12] reported that Blockade of CTLA-4 and PD-1 (PD-L1) antibodies enhances immune responses against tumor cells in a variety of cancer forms. Although these blockades are currently used to treat colorectal, prostate, lymphoma, melanoma, lung and mesothelioma cancers, as well as renal cancer, research into their effectiveness in other cancers is ongoing [13,14].

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Immunotherapy and cancer treatment

The immune system recognises foreign materials and eliminates them through immunological reactions. Immunotherapy is an advancement in cancer treatment options. It is a good example of precision medicine because it utilises a more specific approach than traditional cancer treatment methods; surgery, chemotherapy, and radiation. It uses the immune system in fighting cancer. Loose and Wiele [15] reported that novel methodologies in cancer immunotherapy are developed from enhanced knowledge of immune recognition, regulation and tumour escape in line with tumour biology and immunology. Tumours can be generated from weak immunologic cancer cells [16], while high immunogenic variants can be eliminated in immune-competent hosts due to immune-surveillance [17].

Immunogenic cancer types are identified by the noting that they are more common in immunocompromised people who are treated with immunosuppressive drugs. Tumor immunogenicity is determined by the tumor cell itself, as well as factors in the tumor's microenvironment, like the role of competent antigen-presenting cells (APCs) such as Dendritic Cells (DCs) [18]. Tumour antigenicity and antigen processing and efficiency presentation are essential determinants of tumour immunogenicity [19]. Thus, in an immunosuppressed population, the APCs, and antigen processing of cancer cell types may serve as indicators and markers of their presence. Also, immune cells interaction with tumour cells could be sub-type specific. Lhuillier, et al. [20] suggest that a higher load of mutation elicits tumour-specific antigen production in high levels and can engender stronger immunological responses. When compared to the luminal A and B subtypes, triple-negative breast cancer (TNBC) and human epidermal growth factor receptor 2 (HER2-positive) breast cancer has more genomic instability [21], thus an to increased DNA damage [22].

During tumor growth, the immune system interacts with cancer cells and goes through three phases: elimination, equilibrium, and escape. In the elimination/immunosurveillance phase, effector immune cells recognize tumor antigens and destroy cancer cells [23]. There are three roles of elimination in tumour prevention. First, is through viral suppressive mechanism or viral elimination mechanism. Some viral infections induce cancer [24]. Next, is through pathogen elimination mechanism to prevent an inflammatory environment that aids tumourigenesis. The last role of elimination in tumour prevention is via the tumour cells identification and elimination mechanism on the expression of Tumour-Specific Antigens (TSAs). Patients with pre-existing anti-tumour immunity and a higher number of tumour infiltrating T cells have a better chance of surviving longer [25]. Furthermore, it's been proposed that the presence of effector immune cells in premalignant lesions serves as a counterbalance to danger signals [25].

Immune-suppressive mechanisms and alternatively activated type-2 macrophages (M2)) maintain a balanced number of effector immune cells in the equilibrium process (e.g. regulatory T cells (Tregs), Myeloid-Derived Suppressor Cells (MDSC). Tumour-infiltrating cells play a role in cancer immune response modulation [26]. Tanchot, et al. [27] found that when Tregs are found in the blood and microenvironment of different tumor types, they interfere with the innate and adaptive immune systems by suppressing T-cell response and Natural Killer (NK) cell proliferation and function. Immune-suppressive pathways outcompete effector immune cells during the escape process, resulting in cancer immune evasion and tumor development [20,28]. The seventh hallmark of cancer [5] is immune-surveillance evasion, and the mechanism by which this is accomplished is addressed in the subsequent outlines.

Mechanisms of cancer immune evasion

Through the expression of tumour variants and suppression of immune environment, cancer cells evade immune attack. In this article, the mechanism by which T-cells destroy cancer cells is first discussed before cancer immune evasions'.

T-cell receptors are activated as they bind to antigen peptides on the Major Histocompatibility Complex (MHC). CD8+ (Cytotoxic T-Lymphocytes) CTLs are activated after antigen recognition by MHC I and can destroy targeted cancer cells using death cell ligands including Tumour Necrosis Factor Apoptosis-Inducing Ligand (TNF- RAIL) or the perforin/granzyme pathway [29,30]. Adaptive cancer immunity is also ensured when CD4+ T cells recognize MHC II-presented peptides [31]. CD4+ T cells can help dendritic cells (DCs) induce CTLs, and cytokines like Interleukin-2 (IL-2) can help activated CTLs expand clonally [32]. Activated CD4+ T cells improve the function of innate immunity cells, such as macrophages and NK cells, by secreting more Interferon-Gamma (IFN-γ). [33]. Figure 1 below shows the mechanism of tumour immune evasion.

Role of MHC I and IFN signaling

Tumor cells downregulate MHC I molecules, proteasome subunit LMP 2 and LMP7, and transporter associated with Antigen-Presenting Protein (APP) in order to avoid being recognized by CD8+ CTLs and destroyed (Fig. 1). IFN-induced signaling facilitates antigen presentation in tumor cells, and Aplnr and Ptpn2 and CDK4/6 have recently been found to upregulate and downregulate IFN signaling, respectively [23]. Upregulation of Ptpn2/CDK4/6 and the downregulation of IFN signaling/Aplnr can dampen antigen presentation and contribute to tumor immune evasion [34-36]. As a result, Aplnr's upregulation of IFN signaling and Ptpn2's and CDK 4/6's downregulation facilitate antigen presentation and immune checkpoint blockade.

Concerted efforts from CTLA-4, PD-1 and PD-L1

These molecules can both inhibit T-cells and activate immunosuppressive regulatory T-cells, making them important tools for controlling T-cell activity and proliferation. The Tumour Microenvironment (TME) and lymphoma cells both express PD-L1, while PD-1 is mainly expressed in the T-cell microenvironment. T cell exhaustion is caused by cancer cells increasing PD-L1 and PD-1 expression or promoting PD-L1 and B7-1/2 binding to the immune checkpoint proteins

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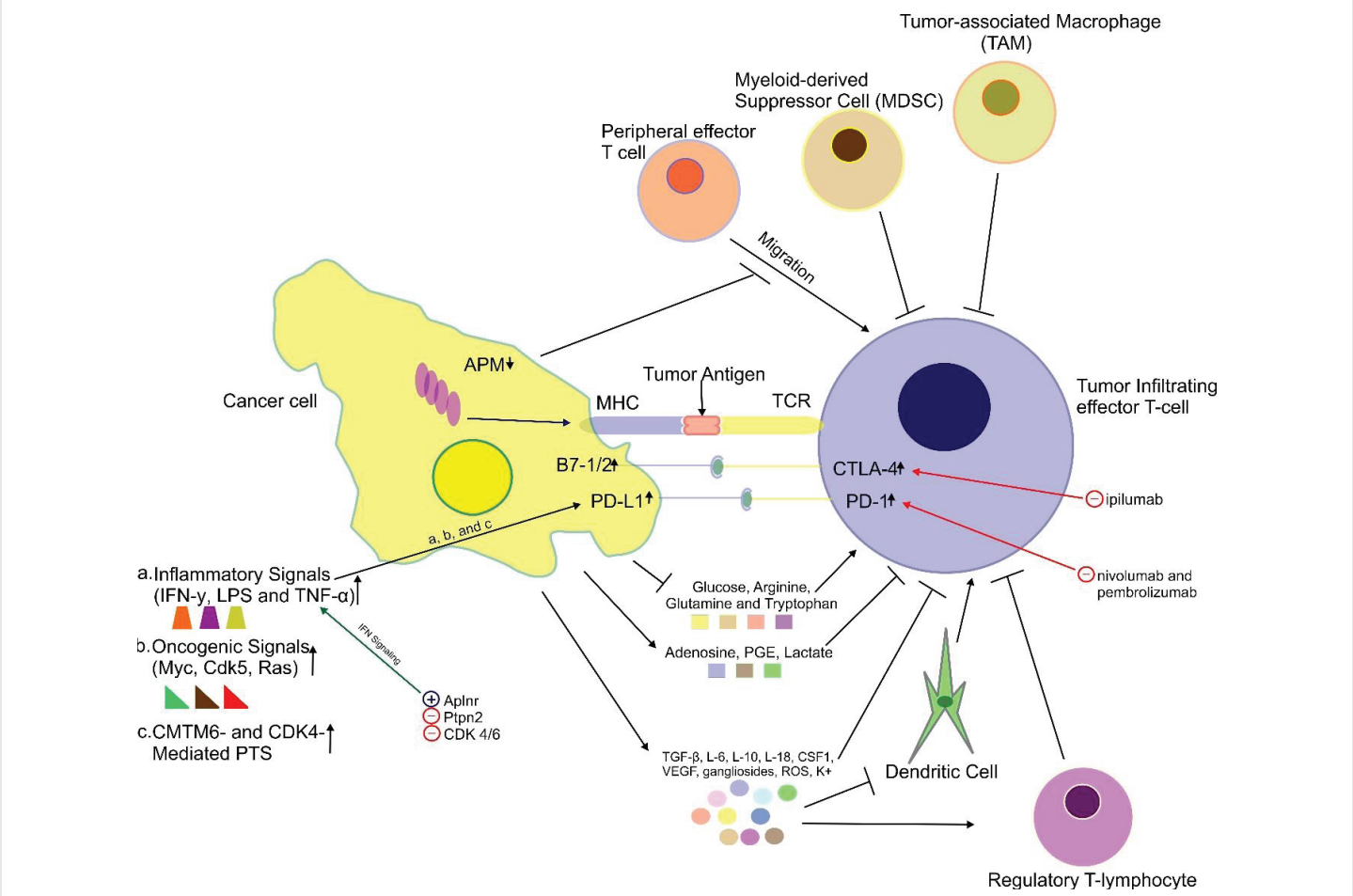

Figure 1: Illustration of cancer immune evasion mechanisms.

PD-1 and CTLA-4 [28,37]. CTLA-4 is a member of the immunoglobulin superfamily. CTLA-4's main function is T-cell inactivation, which is accomplished by two distinct pathways. Upregulation of inflammatory signals (such as IFN-, LPS, and TNF-), oncogenic signals (Myc, Cdk5, Ras), and CMTM6- and CDK4-mediated post-translational stabilization contribute to T cell exhaustion via PD-L1 expression [38]. T-lymphocyte fatigue, on the other hand, may be caused by KEAP/PTEN downregulation. Immune evasion is often due to tumour cells secreting immune-suppressive molecules into the Tumour Microenvironment (TME) (e.g. IL-8, IL-10, IL-18, VEGF, gangliosides, ROS, TGF-, and K+) [23].

Alteration of metabolic functions

The alteration in metabolism is one of the hallmarks of cancer cells. Similarly, tumor cells can impair T-cell function by changing metabolic activities in the TME. Carbohydrate metabolism (such as glycolysis, Kreb's cycle, and Pentose phosphate pathway), amino acid metabolism, lipid metabolism, and nucleotide metabolism are all altered in the TME to improve cancer survival. Tumour cells reduce factors that promote T cell activity, such as oxygen, pH, and biomolecules, while simultaneously increasing the concentration of molecules that inhibit T cell function, such as adenosine, Prostaglandin E (PGE), and lactate [23]. Tumour cells have a higher rate of glucose oxidation, resulting in lower glucose supply in the TME [39,40]. Tripartite motif 47 (TRIM47) also speeds up aerobic glycolysis and tumor progression in pancreatic cancer by controlling fructose-1, 6-biphosphatase (FBP1) ubiquitination Lei, et al. [41]. This happens because cancer cells require energy in the form of ATP to proliferate, expand, invade, and spread (Figure 2). Fatty acid synthesis, amino acid synthesis, and nucleic acid synthesis all take place during glycolysis. Often, for the same reason, amino acids like glutamine are used to replenish substrates in the Tricarboxylic Acid Cycle (TCA). Glycolysis occurs at a faster rate in cancer cells than in normal.

Furthermore, immune suppressive cell populations in TME are a key contributor to T cell dysfunction. Tregs coordinate a T-cell dysfunction system in which suppressive modulators (e.g. TGF-, IL10, gangliosides), metabolites (e.g. PGE), MDSC, and tumor-associated macrophages (TAM) improve its activity [28].

Cancer immune evasion is caused by complex interactions that take place at the immune checkpoint. Immune checkpoint blockades work by blocking or inhibiting the pathways that cause immune evasion by causing T-cell dysfunction.

Immune checkpoint inhibitors

Immune checkpoint inhibitors (ICPIs) have led to significant advances in cancer care. Immune checkpoint inhibitors improve anti-tumour immunity by inhibiting negative pathways that

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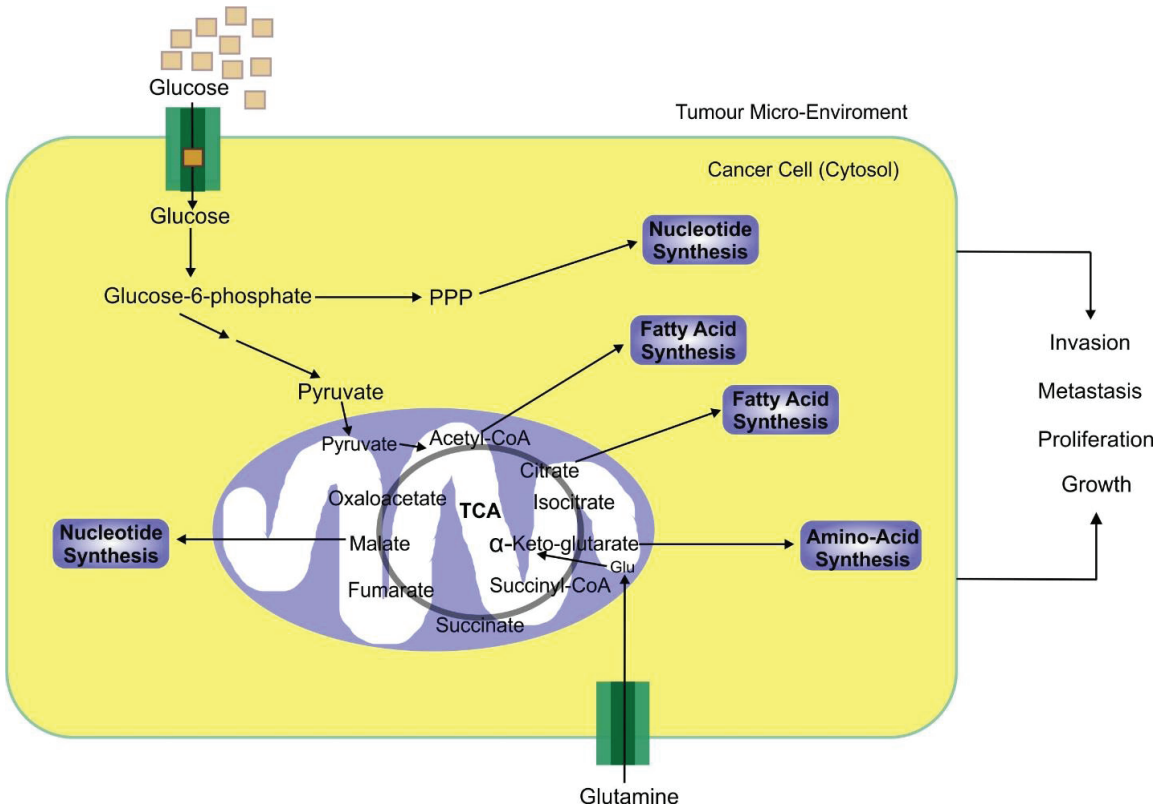

Figure 2: Glucose metabolism regulation in cancer cells.

prevent T cells from working properly. As a result, blockades with antibodies against CTLA-4, PD-1, or their respective ligands, B7-1/2 and PD-L1, improve immune responses against tumor cells [42], as their upregulation is linked to an increased risk of cancer [6,44].

Anti-PD-1 (nivolumab and pembrolizumab), anti-CTLA-4 (ipilimumab), and anti-PD-1/CTLA-4 (nivolumab–ipilimab) immunocheckpoint inhibitors have improved cancer care. Pembrolizumab and nivolumab, anti-PD-1 inhibitors, are superior to ipilimumab, an anti-CTLA-4 inhibitor, in terms of overall and progression-free survival in the first-line environment [43,44]. Anti-PD-1 (nivolumab and pembrolizumab), anti-CTLA-4 (ipilimumab), and anti-PD-1/CTLA-4 (nivolumab–ipilimab) immunotherapy regimens result in a higher response rate and longer time to progression than either agent alone [44]. Studies in advanced melanoma have the most justification for the use of ICPIs [10]. In cancer patients with resected stage III melanoma, ipilimumab improves survival [45].

CTLA-4 inhibition

CTLA-4 is a member of the CD28:B7 immunoglobulin superfamily, which is expressed on the membranes of effector T-cells and Tregs [46]. The first signal for T-cell activation is the recognition of the MHC-bound tumour antigen by a specific T-lymphocyte receptor. The co-stimulatory involvement of CD28 receptor on T cells by B7 on Antigen Presenting Cells (APC) occurs after full T-cell activation [47]. There are assumptions that anti-CTLA antibodies engender tumour rejection by inhibiting negative signals from B7-CTLA-4 interactions [48]. However, it has been reported that the anti-CTLA-4 antibody Ipilimumab does not block the B7 trans-endocytosis plasma levels when its concentrations are considerably higher than that of the plasma levels [48]. CTLA-4 is upregulated after a naive T-cell is stimulated, competing with CD28 receptor for B7, and ultimately suppressing T-lymphocyte function. As a result, CTLA-4 monoclonal Antibody (mAb) promotes T-cell activation, functionality, and proliferation while inhibiting Treg suppressive activity [49]. In metastatic melanoma, ipilimumab was the first CTLA-4 blockade to demonstrate an improved survival rate [50,51]. CTLA-4 is a main receptor found on the surface of T lymphocytes that sends an inhibitory signal to T lymphocytes through its ligand B7-1/2, inhibiting T-cell activation [52]. As a result, blocking CTLA-4 eliminates the inhibitory signal, resulting in increased T-cell activation.

PD1/PD-L1 inhibition

Tumor cells and myeloid cells in the host can also express the immunosuppressive ligand PD-L1. T-cells express PD-1, which binds to PD-L1, which is expressed on cancer cells, and PD-L2, which is expressed on other immune cells. Since PD-L1-expressing cells can cause activated T lymphocytes to die by binding PD-L1 to the cognate receptor PD-1 (CD279) on T cells, PD-L1-mediated inhibition of activated PD-1+ T-lymphocytes is thought to be a major immune evasion mechanism in tumor cells. Blocking PD-L1/PD-1 signaling prevents tumor growth by reducing tumor-induced immune suppression. PD-1 antibodies like nivolumab, pembrolizumab, and pidilizumab, as well as PD-L1 antibodies like Durvalumab MEDI4736 and

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Atezolizumab MPDL3280A, enhance T-cell response and sensitivity to cancer by inhibiting PD-1 and PD-L1 binding [53].

To ensure immunological memory [54], a portion of effector T-lymphocytes differentiates into effector memory T-lymphocytes. These cells are responsible for combating diseases that recur. Reactivation and clonal proliferation of memory T-cells present in the TME are needed for immune responses against tumors following PD-1/PD-L1 blockade [55,56]. Tumour-specific CD8+ T-cells then differentiate into effector T-cells, proliferate, migrate to the TME, and destroy tumor cells that present tumor-associated antigen on HLA by releasing cytolytic effector molecules [55].

Although these blockades aid in the prevention of T-cell fatigue, they can sometimes cause side effects known as "Immune-related adverse events (IrAEs)."

Immune checkpoint blockades toxicity

The toxicity of this cancer immunotherapy alternative has been a significant challenge and source of concern [6]. IrAEs from ICPIs are caused by a lack of T-cell inhibition, which results in decreased self-tolerance. Checkpoint drugs also cause hyperprogression that can be Fc receptor mediated. Hyperprogressive disease (HPD) is associated with the use of immune checkpoint inhibitors (ICI). HPD-associated -ICI has been reported by multiple groups in various cancer types and this has been linked with a shorter progression free survival and overall survival [57]. The most common irAEs linked to anti-CTLA-4 Ab use can affect any organ system, but gastrointestinal, dermatologic, hepatic, and endocrine toxicities are the most common [58]. These side effects can be treated, but in some situations they can be fatal [50,59,60]. These side effects were observed in two-thirds of patients treated with ipilimumab, and significant toxicities were found in one-tenth to one-fifth of the patient population [50].

After cancer therapy, the initiation of suspected irAEs must be timed carefully. The skin effect in melanoma patients treated with ipilimumab normally appears within the first few weeks of treatment. Diarrhoea and colitis, on the other hand, typically appear between the fifth and tenth weeks, liver toxicity between weeks seven and fourteen, and hypophysitis after six weeks [58]. The majority of ipilimumab-related irAEs occur during the induction period [61], but some patients who are exposed to ICPIs may experience late-onset irAEs after treatment [62,63]. When compared to anti-CTLA-4 Ab like ipilimumab, PD-1 inhibitors like nivolumab and pembrolizumab have a lower incidence of irAEs [64]. Pembrolizumab also has a nine-week median initiation of mild to extreme toxicity, compared to six weeks for ipilimumab [23]. The combination of nivolumab and ipilimumab would result in a higher rate of irAEs than either drug alone.

In comparison to ipilimumab, pembrolizumab has a nine-week median onset of moderate to severe toxicity, compared to six weeks for ipilimumab [23]. Nivolumab and ipilimumab in combination would result in a higher incidence of irAEs than either drug alone [58]. In the following chapters, we'll go through the dermatological, endocrine (endocrinopathy), hepatic (hepatoxicity), and diarrhoea/enterocolitis-related toxicity of ICPIs.

Dermatologic toxicity

Maculopapular rash, erythematous rash, and pruritus are the most common dermatologic toxicities [6]. Dermatologic toxicity is most common in the first few weeks of treatment [42], but it has also been noted to appear later [65]. It is more common in advanced melanoma patients than in patients with other cancers. In a meta-analysis of patients treated with ipilimumab, Minikis et al. found that 24.3 percent developed a rash, with 2.4 percent being high-grade. Anti-CTLA-4 and anti-PD-1 mAbs have been linked to vitiligo, a skin condition. Abs clinical trials [67] can also be found and is generally considered a good prognostic factor in patients with melanoma; it occurs through the production of anti-melan-A T-lymphocytes unique to an anti-melanoma immune response; it occurs through the development of anti-melan-A T-lymphocytes specific to an anti-melanoma immune response [68]. Despite the rarity of serious skin toxicity, Stevens-Johnson syndrome, toxic epidermal necrolysis, and drug rash with eosinophilia and systemic symptoms have been reported [69]. The highest rates of serious skin toxicity are seen with combination immunotherapy [44]. Immunosuppressive treatment should be stopped in this case; topical steroids may be effective for mild symptoms, but prednisolone may be used in extreme cases. Even, emollient creams, avoidance of additives and sun safety were recommended preventive measures for all patients [12].

Endocrinopathy

Endocrine toxicity caused by ICPIs can range from asymptomatic changes in thyroid function tests to adrenal problems. Endocrinopathy may be mistaken for other disorders such as brain metastasis, sepsis, or disease progression because of its non-specific symptoms. Endocrine toxicity normally appears after 10 weeks with nivolumab and seven weeks with ipilimumab [42,70]. Hypophysitis and hypothyroidism are the most common endocrinopathies associated with immune checkpoint inhibitor therapy [67]. It is also recommended that thyroid functions be adequately assessed before starting ICPI treatment.

Fatigue, headaches, and visual field defects are common symptoms of hypophysitis, and its diagnosis is based on pituitary hormone levels (ACTH, TSH, FSH, LH, GH, and prolactin) [71]. Patients with hypophysitis caused by ipilimumab may be given pembrolizumab [72]. Hypophysitis is characterized by a reduced TSH and a low free T4, whereas hypothyroidism is diagnosed by an elevated TSH and a low free T4. It's also worth noting that primary hyperthyroidism has a lower frequency of CTLA-4 and PD-1 inhibition than hypothyroidism [67].

Hepatotoxicity

Various ICPI trials have used the words hepatitis, elevated transaminases, and bilirubin to characterize liver dysfunction, which normally occurs between 6 and 14 weeks after starting therapy [12]. According to Viladolid and Amin [67], both CTLA-4

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and PD-1 inhibitors induce autoimmune hepatotoxicity, which presents as elevated transaminases and complete bilirubin, with a median onset of 8-12 weeks after treatment initiation.

Anti-PD-1 agents cause hepatitis in 1–6% of patients, while ipilimumab and the combination cause hepatitis in 1–7% and 30% of patients, respectively [23,44,60]. In patients with ALT or AST levels greater than five times the upper limit of normal, steroid therapy should be used [12]. As a result, a liver function test is needed before each dose of ipilimumab, nivolumab, or pembrolizumab to control hepatic function [42,73].

Diarrhoea/Enterocolitis

Diarrhoea and colitis may occur six weeks after starting ICPIs, and the dosage of ipilimumab appears to be a factor [50,51]. Following ipilimumab therapy, patients who were given PD-1 blockers did not experience diarrhoea or colitis [42,72]. Often, following pembrolizumab treatment, hyperglycemia from type 1 diabetes mellitus occurs, and a case of diabetic ketoacidosis complicates nivolumab therapy [74,75].

Though enteritis has been linked to CTLA-4 inhibitors, it is uncommon [70]. The word "colitis" refers to diarrhoea that is accompanied by abdominal pain, rectal bleeding or mucous, or large bowel inflammation. Patients treated with both ipilimumab and nivolumab would have median onset of diarrhoea at 7 weeks, according to Bristol Meyers Squibb [76] product information, while Merck-Sharp [76] product information states that it tends to be about 6 months with pembrolizumab [77-83]. If diarrhoea or colitis recurs after treatment, the ICPI should be discontinued [12].

Conclusion and future direction

Cancer immunotherapy is considered as one with precision due to its specificity in action. It is presumed safer than the traditional therapeutic options, as discussed earlier. While biomarkers for predicting patients' response to immunotherapy could be researched, in-depth understanding of cancer immune evasion will help develop effective Immune-checkpoint inhibitors. IrAEs are a common side effect of ICPIs, some of which are serious but are normally reversible if detected early. A focus on combined therapies that will aid the inhibitors' effectiveness while reducing irAEs to the barest minimum is essential. Majority of operations evident on the immunological scale has a genomic stand-point. Hence, genome sequencing technology seems to be a promising approach to studies on the immune system function and dysfunction; immunogenomic research on cancer will help reveal mechanisms behind the action and response of tumour infiltrating effector T-lymphocytes, and also the synthesis and corrections of genes coding for immune cells. This approach will engender enhanced advancement in cancer immunotherapy.

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