Chapter

Role of Immunosuppressive and Immunomodulatory Agents in Cancer

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Abstract

Immunosuppressants offer some benefits and disadvantages. Like a blade with two edges, immunosuppressants are categorized as drugs but also cause decreased immunity, which eventually cause cancer. Immunosuppressants are widely used in organ transplantation patients and autoimmune illnesses to suppress the immune response and provide a significant risk of cancer. According to epidemiological and cancer research, malignancies are higher among transplant patients. However, the risk varies significantly between studies due to methods and patient selection variations. A more accurate illustration of the effects of mild-to-moderate immunosuppression concerning the risk of cancer can be seen in the rising use of immunosuppressant medications in non-transplant patients. Generally, cancer cells have an approach to avoid immune surveillance and create a complex balance in which many immune subtypes may be responsible for controlling tumor development, metastasis, and resistance. Therefore, the main objective of most cancer immunotherapies is to reestablish effective immune control. Immunomodulators help to maintain immune system function and promote the immune system's capacity to fight and defeat cancer. One of them is immune checkpoint inhibitors.

Keywords: immune system, immunosuppressant, immunomodulator, immune checkpoint inhibitor, cancer

1. Introduction

Malignancies are reported to be linked with the immune suppression system. Consequently, approximately, about 8.2 million annual casualties are expected to increase [1]. The concept, innate and adaptive immune cells can regulate tumor growth. However, neoplasm tissue tumors are identifiable as malignant cells and evolve new defense mechanisms that imitate peripheral immunological tolerance to fight against tumoricidal strikes [2]. In addition, due to the cancerous cells having antigens that make them different from normal cells, the immune system can find cells that have become cancerous [3]. The immune system recognizes and eliminates

abnormal cells as part of its normal function, most likely preventing or slowing cancer progression [4].

Present chapter discusses the significance of comprehending the immune system's function in the emergence of cancer, including the often prescribed immunosuppressant medications for autoimmune and organ transplant patients. Also, this manuscript shows the importance of the immunomodulators, including immune checkpoint blockade, in cancer immunotherapy.

2. Cancer and immune suppression

The host immune system is well established to contribute to the evolution and progression of cancer, as significant as the tumor immune system. The complex interactions between the immune system and the tumor commonly occur in either the tumor's immune deterrence or the termination of cancer [5]. Moreover, significant discoveries in the last few decades have demonstrated that the immune system plays an important role in maintaining the equivalence between immune recognition and cancer development. And it might both promote and inhibit tumor growth [6].

Immune cells that have entered the tumor microenvironment (TME) regulate the growth and dissemination of cancer (TME) [7]. The disruption of the TME induces an inflammatory immune response, as evidenced by the presence of innate and adaptive immune cells in histopathological examinations, and is classified as tumor growth [8]. Interactions between the morphological and molecular elements of the TME through a complex and multistep metastatic cascade enable cancer cells to spread from the initial site to distant regions and become invasive [9]. Immune evasion also frequently occurs due to interactions between the elements of the immune system and the tumor cells in the TME, which promotes the development of tumors [10].

Tumor formation is initiated when immune cells like CD8+ T cells and natural killer (NK) cells attack and destroy most cancer cells. However, specific tumor cells can avoid these immune defenses by suppressing effector cells or stimulating tolerogenic cells during the immunological escape period. External and internal mechanisms that reduce antitumor immune responses and increase immunosuppressive cells, like regulatory T cells (Treg) and myeloid-derived suppressor cells (MDSCs), promote immune surveillance escape [11]. Regulatory T (Treg) cells expressing Foxp3+ reduce the dysfunctional immune response to self-antigens and the antitumor immune response. Additionally, Treg cell infiltration into tumor tissues is frequently associated with poor clinical outcomes [12]. Autoimmune diseases occur when Treg cells are insufficient due to immune suppression of Foxp3+, CD25+, and CD4+ Treg cells; these cells have been identified as one of the most important mechanisms of immunological self-tolerance [13]. In addition, a study has shown that Treg cell ablation can induce antitumor immunity effectively. However, it can also result in autoimmunity, particularly if Treg cells are eliminated systemically [14].

Treg cells have the ability to regulate T-cells, B-cells, NK cells, dendritic cells (DCs), and macrophages via humoral and cell–cell contact pathways. Several molecules, including TGF (transforming growth factor), GITR (glucocorticoid-induced TNF receptor), CTLA-4 (cytotoxic T-lymphocyte-associated protein 4), LAG3 (lymphocyte-activation gene 3), IL-2, IL-10, IL-35, granzyme B, adenosine, and cAMP, are implicated in Treg-mediated suppression pathways [15]. Foxp3+ regulates the expression of these molecules, and deficiencies of IL-2, CD25, CD122, and CTLA-4 are associated with autoimmune disorders. According to these hypotheses, only a few

molecules have their expressions directly or indirectly regulated by Foxp3+, such as IL-2, IL-2 receptor subunits, and CTLA-4. The absence of these molecules results in severe autoimmune disorders and the loss of Treg-suppressive function [16–18].

In addition, the suppression mechanisms dependent on Tregs are necessary for establishing self-tolerance and have a significant impact on tumor immunity. The expression of CD25 and CTLA-4, dependence on exogenous IL-2, and T-cell receptor (TCR) activation produce Treg functions, particularly suppression mediated by Tregs. Regarding tumor immunity, these molecular mechanisms are also effective targets for regulating the activity and expansion of Tregs [16]. Therefore, recent advances in cancer immunotherapy targeted Treg cells suggest that Treg depletion or functional modification may be facilitated by Treg-specific drugs. These molecules are CD25, GITR, OX-40, and LAG3 [12]. CTLA-4, programmed cell death receptor-1 (PD-1), and programmed cell death ligand-1 (PD-L1) will be discussed further in this chapter.

3. Cancer and immunosuppressive agents

Since their discovery, many immunosuppressive medications have been used in transplantation and autoimmune diseases. Many organ transplant recipients, for instance, take medication to suppress their immune systems and reduce the graft rejection episodes. The immunosuppressive therapy after transplantation aims to prevent acute and chronic rejection while reducing adverse pharmacological effects in transplant recipients. The majority of therapies modify immune response mechanisms but lack immunological specificity [19].

Any immunosuppressive medication carries a potentially serious risk of cancer. Due to the increasing use of immunosuppressive medications among transplant and non-transplant patients, it is possible to define the effects of mild-to-moderate immunosuppression on the risk of neoplasms [20]. The use of immunosuppressive drugs in organ transplant patients is associated with a wide range of adverse side effects. The potential cancer risks—well-documented since the late 1960s—represent a significant cause of morbidity, mortality, and late failure in patients who otherwise have healthy grafts. Since transplantation first became popular, two agents have been utilized: azathioprine and corticosteroids [21]. Tacrolimus, cyclosporine, mycophenolate mofetil, everolimus, and sirolimus are the most common immunosuppressive drugs used in the combination therapy [19].

Cancers in transplant patients have been the subject of the current study, collecting information from single and multicenter studies. The type of malignancies and estimated risks differ significantly from study to study due to a variety of factors, including geographic differences, the use of various immunosuppressive regimens and antiviral therapy prevention, the duration of follow-up, the type of organ transplant and multiple techniques for estimating the occurrence [20]. The malignancy incidence in transplant recipients is higher in young adults, with significant clinical aggressiveness and a relatively short time in initiation after transplantation. Additionally, a key risk factor for immunosuppressive medication use is the dosing frequency and schedule [22].

A high prevalence of cancer among transplant recipients was seen/observed. Still, there is a debate over which factors—such as the type of immunosuppressive regimens, the overall level of immunosuppression, the course of treatment, or the dosage—is most important to assess the risks involved. The early agent used,

azathioprine, can potentially cause cancer directly or indirectly. A study in premalignant dysplastic keratotic lesions showed that azathioprine might have a carcinogenic effect rather than simply suppressing the immune system [23]. Although cyclosporine unexpectedly showed the high rates of lymphomas and Kaposi's sarcomas, there is no substantial evidence that this medication increases the risk of tumors compared to those seen with the other immunosuppressive drugs such as, traditional azathioprine-based regimens [24]. On the other hand, tacrolimus-induced post-transplant malignancies were shown to have a high prevalence and pathological characteristics comparable to other immunosuppressive drugs [25].

In addition to treating non-transplant patients, such as Inflammatory Bowel Disease (IBD), immunomodulators such as thiopurines or methotrexate and TNF-antagonists may also reduce the incidence of inflammation-related cancers. However, although there is little chance of developing cancer when taking azathioprine in non-transplant patients, there is a potential risk that may rise with time and in a dose-dependent manner [26]. Although cyclophosphamide is typically used for cancer patients or bone marrow transplantation regimens, its immunosuppressive effects have also been applied to many chronic inflammatory diseases. For example, in people treated for cancer or non-malignant illnesses, it was shown to have the ability to increase the risk of bladder cancer. However, long-term cyclophosphamide therapy in a non-neoplasm patient is linked to an increased frequency of some malignancies, suggesting an immunosuppressive agent's potential side effect [27].

Immunomodulators and biological agents affect the immune system and might promote cancer development [28]. Thiopurines and methotrexate contribute to the development of the cancer by activating oncogenes, altering DNA directly, reducing physiologic immunosurveillance of malignant cells, and impairing the immune system's capacity to regulate oncogenic viruses [27, 29]. Infliximab, a chimeric IgG antibody, is primarily directed against TNF-α to neutralize the cytotoxic effects in a dose-dependent manner and has recently been licensed to treat rheumatoid arthritis and Crohn's disease [20]. However, TNF-α has many different impacts on the immune system, but the carcinogenic potential is less understood because of unreliable molecular information. TNF-α has been demonstrated to have antitumor activity by inducing the cellular death of malignant cells. Moreover, as a pro-tumor inflammatory cytokine, TNF-α is generated by most tumors to stimulate cellular survival and accelerate cancer growth [30, 31].

Another immunosuppressant agent that is used in the transplant population is Rapamycin. Streptomyces hygroscopicus is the source of the fermentation product rapamycin (RAPA), also referred to as sirolimus [32]. Many studies revealed that RAPA was a potent immunosuppressive drug to prevent allograft rejection in the heart, liver, lung, and kidney transplantation [33–35]. Sirolimus, and its analogs, including deforolimus, everolimus, and temsirolimus (a rapamycin prodrug), block the mechanistic target of Rapamycin (mTOR). Therefore, rapalogs are used in some clinical applications, such as organ transplant management and cancer therapy. The immunosuppressive properties of Rapalogs justified their use in organ recipients. Despite the fact that rapalogs were predicted to promote tumor growth and increase cancer incidence, they are frequently used in cancer treatment [36].

Commonly, growth factors, nutrient-rich environments, and oxygen levels excessively stimulate cultured cells. The environment stimulates growth-promoting pathways, including the PI3K/mTOR axis and mitogen-activated protein kinases (MAPKs). The activation of the oncosuppressor p53 and the accumulation of cell cycle inhibitors, such as cyclin-dependent kinase inhibitor 1A (CDKN1A) and

cyclin-dependent kinase inhibitor 2A, can induce a cell cycle arrest under certain stress conditions (CDKN2A). In the case of malignant cells, growth factors and oncogenic signaling pathways continue to activate cultured cells by promoting mTOR and MAPK signaling even though the cell cycle has finished [37, 38]. Therefore, rapalogs are increasingly recommended for cancer treatment, especially for mTOR-dependent cancer subtypes [39, 40]. Thus, rapalogs could be thought of as anti-inflammatory substances that demonstrated anticancer. In addition, Rapamycin and its analogs also lowered the risk of cancer related to organ transplants and extended the overall and disease-free longevity of patients with certain malignancies.

4. Immune checkpoint inhibitors (ICI) as immunomodulatory agents

In adaptive immunity, two immune cells, B and T. B-cells, recognize circulating antigens in their natural state and produce protective antibodies in response [41]. T-cells are a powerful weapon the immune system uses to fight cancer [42]. T-cells identify peptide antigens from intracellularly degraded proteins filled onto the Cell's surface of *major histocompatibility complex (*MHC) molecules, and this process is known as antigen presentation [43]. Immunological checkpoints on the cell surface are activated when their surface proteins recognize and bind to partner proteins on other cells, such as specific tumor cells [42]. Self-tolerance requires immune checkpoints to prevent autoimmunity and protect tissues from destruction [44]. Tregs are drawn to cancer cells, which causes them to express less tumor antigen and release immune-suppressive cytokines that activate inhibitory immunological checkpoints [10] that create an immunosuppressive TME [45]. Immune checkpoint inhibitors work by obstructing particular inhibitory pathways' actions to combat immunosuppressive conditions [44]. The "brake system" of the immune system that cancers routinely exploit to halt immunological responses and defend themselves are immune checkpoints. Checkpoint inhibitors can generate new immune responses against cancer and strengthen already-existing ones to remove malignant cells.

The CTLA-4, PD-1, and PD-L1 are the common inhibitory checkpoints [46]. These antibodies have biological effects on different body parts during the T cell's lifecycle [47]. In addition, they functionally complement one another, establishing that T cell responses retain self-tolerance while defending the body from infections and cancer [43]. The immune checkpoint inhibitors approved by the FDA are shown in **Table 1**.

4.1 CTLA-4

In humans, CTLA4 is the first immune-checkpoint receptor to be studied; its located on T cells and controls T cell activation in the early stages of infection [48]. *CTLA-4* is a novel immunoglobulin superfamily member resembling CD28, structurally and pharmacologically [49]. CTLA-4 and CD28 are expressed exclusively in the hematopoietic compartment and found in the exact location of chromosome 2 (2q33.2). Furthermore, CTLA-4 and CD28 have the most sequence similarity in their extracellular binding domain; they bind to the identical CD80 and CD86 ligands expressed by antigen-presenting cells (APCs) [50]. Further characterization revealed that CD28 and CTLA4 have opposing immunoregulatory functions. CTLA4 inhibits T cell activation in a number of ways, including by directly opposing CD28, competing for co-stimulatory ligands, preventing the production of immunological conjugates,

Target	Drugs	Mechanism of action	Approval year	Treatment
CTLA-4	Ipilimumab	Inhibited CTLA-4, T-cell activation	2010	CRC, HCC, melanoma, mesothelioma, NSCLC, RCC
PD-1	Nivolumab	Inhibited PD-1, T-cell activation	2014	CRC, esophageal SCC, HCC, HL, HNSCC, melanoma, mesothelioma, NSCLC, RCC, UC
	Pembrolizumab	Inhibited PD-1, T-cell activation	2014	BC, CVC, CRC, CSCC, EnC, EsC, GC, HCC, HL, HNSCC, melanoma, mesothelioma, MCC, NSCLC, LBCL, RCC, SCLC, UC
	Cemiplimab	Inhibited PD-1, T-cell activation	2018	BCC, CSCC, NSCLC
	Dostarlimab	Inhibited PD-1, T-cell activation	2021	dMMR, EnC
PD-L1	Atezolizumab	Inhibited PD-L1, T-cell activation	2016	BC, HCC, melanoma, NSCLC, SCLC, UC
	Avelumab	Inhibited PD-L1, T-cell activation	2017	MCC, RCC, UC
	Durvalumab	Inhibited PD-L1, T-cell activation	2018	NSCLC, SCLC, UC

CRC, colorectal cancer; HCC, hepatocellular carcinoma; NSCLC, non-small cell lung cancer; RCC, renal cell carcinoma; BCC, basal cell carcinoma; CSCC, cutaneous squamous cell carcinoma; EnC, endometrial carcinoma; EsC, esophageal carcinoma; GC, gastric carcinoma; SCC, squamous cell carcinoma; HL, Hodgkin lymphoma; HNSCC, head, and neck squamous cell carcinoma; UC, urothelial carcinoma BC; Breast cancer; CVC, cervical cancer; MCC, Merkel cell carcinoma; LBCL, large B cell lymphoma; SCLC, small cell lung cancer; dMMR, mismatch repair deficient.

Table 1.
Immune checkpoint inhibitors approved by FDA.

and recruiting inhibitory effectors [51]. Moreover, CTLA4 promotes the internalization of its ligands, which prevents them from binding to CD28 and reduces IL-2 production and T-cell proliferation [52].

4.2 Clinical application of CTLA-4 inhibitor

In 2010, the FDA authorized ipilimumab for advanced melanoma treatment, making it the first medicine with a survival advantage for metastatic melanoma. Long-term studies have shown that antitumor immunity persists following CTLA4 inhibition, confirming the stability of this survival effect [53]. Unfortunately, findings from trials in renal cell carcinoma [54], non-small-cell lung cancer [55], small-cell lung cancer [56], and prostate cancer [57] were less effective than those reported in melanoma patients. The FDA has not yet approved tremelimumab, an IgG2 isotype CTLA4-blocking antibody, because it did not extend survival in patients with advanced melanoma. It is believed that the effectiveness of ipilimumab and tremelimumab differs due to differences in binding kinetics and the ability to mediate cytotoxicity [58].

4.3 PD-1/PD-L1

PD1 was initially considered to be a potential modulator of apoptosis. However, later data revealed a role in regulating hyperactivation of the immune system, like CTLA4 [59]. CTLA4 and CD28 have 20% and 15% amino acid identity, respectively [60]. CTLA4 limits T-cell activation in peripheral tissues, whereas PD1 regulates T-cell activation predominantly within lymphoid organs. Relatively, the PD1 axis performs a particular role in self-tolerance in T cells [47].

4.4 Clinical application of PD-1/PD-L1 inhibitor

Pembrolizumab and nivolumab (both IgG4), humanized and completely human anti-PD1 monoclonal antibodies (mAbs), were the first FDA-approved PD1-targeted therapies for refractory and unresectable melanoma in 2014 [61]. Pembrolizumab exceeded ipilimumab in six-month progression-free survival and overall survival [62]. Pembrolizumab was approved in 2015 for treating non-small-cell lung cancer because it increased progression-free survival by 4.3 months compared to platinum-based chemotherapeutics and was more productive than paclitaxel [63]. However, the different organs have distinct immunosuppressive microenvironments, so it's difficult to anticipate which patients may benefit. Nivolumab has since been approved for treating renal cell carcinoma, head and neck squamous cell carcinoma, urothelial carcinoma, hepatocellular carcinoma, Hodgkin lymphoma, and colorectal cancer, similar to pembrolizumab [64].

PDL1 also targeted several antibodies that have benefits for cancer treatment. Atezolizumab (an IgG4 antibody), the first PDL1-targeted humanized mAbs, was licensed to treat urothelial cancer in 2016 [65]. However, more trial results have not shown that atezolizumab has clinical efficacy in urothelial carcinoma over the standard of treatment, even though it is less toxic than conventional chemotherapy [66]. In 2017, avelumab and durvalumab, two new anti-PDL1 human mAbs, were introduced to the market [67]. As a result, similar to PD1, blocking PDL1 is successful in difficult-to-treat cancers.

4.5 Clinical challenges during the blockade of immune checkpoint

Potent immune effector mechanisms are activated by blocking a naturally occurring immunological checkpoint [68]. According to a meta-analysis study, immune-related adverse events are expected to occur in 15–90% of patients. However, patients treated with CTLA4 and PD1 inhibitors have more severe episodes that require intervention in 15–30% of cases [69]. In addition, patients receiving anti-CTLA4 medication are at a higher risk of hypothyroidism, hepatotoxicity, and pneumonitis. In contrast, the patient that receives PD1-targeted drugs is more likely to develop hypothyroidism, hepatotoxicity, and pneumonitis [70].

Adverse events are particularly problematic in adjuvant chemotherapy because late-onset, frequently severe toxicities can impact tumor-survivor patients even after surgery only [71]. However, the toxicity of immune checkpoint inhibitors is more tolerable than that of conventional chemotherapeutics [72].

5. Conclusion and future perspectives

A decade after immune checkpoint protein discovery, such as PD-1/PDL-1 and CTLA-4, still offers hope for the cure for cancer patients. Although not all patients

may benefit from these medications, some of the drugs demonstrated dose-dependent adverse events of mild to moderate. Unfortunately, not every cancer type responds well to the treatment, and the only options are to discontinue therapy or switch to conventional cancer treatments.

Even though several studies showing the side effects of ICI do not discourage researchers from developing the new finding, these drugs will probably be examined in adjuvant or neoadjuvant approaches, based on clinical responses in various cancer types, to increase the overall survival of many cancer patients. In addition, understanding the systemic effect mechanism caused by immunotherapy may help gain better knowledge for an effective antitumor response. Finally, combination therapy with various immunotherapy, chemotherapy, targeted medicines, radiation, and T-cell-based therapies can potentially improve the outcomes, especially in patients who have not responded well to immunotherapy-based treatments.

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