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Immunological Checkpoint Inhibitors Represent a Novel Approach Within the Realm of Cancer Therapy

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Abstract

The advent of immune checkpoint inhibitors (ICIs) has ushered in a new era in the field of cancer therapy, allowing for the potential of prolonged life in patients with metastatic illness, and offering novel therapeutic applications in the early stages of the disease. Immune checkpoint inhibitors may reinstate the immune system's capacity to combat cancer cells and halt their proliferation by obstructing these proteins. The validity of these results is supported by sufficient clinical trial evidence, and now, many immune checkpoint inhibitors have been authorized by the FDA and are available on the market for the treatment of different kinds of malignancies. They work by inhibiting checkpoint proteins such as CTLA-4, PD-1, PD-L1, etc. They may be used alone or in conjunction with other cancer therapies, such as surgery, radiation, or chemotherapy. In this article, we offer a comprehensive review of these inhibitors and their significance as biomarkers, immune-related bad effects, and their relevance in clinical research for the treatment of different types of malignancies. Additionally, we discuss some potential future possibilities.

Keywords: Immune checkpoint inhibitors, Cancer immunotherapy, CTLA-4, PD-1, PD-L1.

Introduction

The immune surveillance of the tumor regulates and monitors the microenvironment via the innate and adaptive immune systems. Antigen-presenting cells play a crucial part in this monitoring process by recognizing and displaying tumor neoantigens to inactive T-cells. Upon exposure to the antigen, naïve T-cells undergo proliferation and activation, therefore initiating an immune response against the tumor. Both stimulatory and inhibitory signaling molecules regulate this process (1). The suppressive signals are sent by immunological checkpoints, including B and T lymphocyte attenuator (BTLA), programmed death protein 1 (PD-1), and cytotoxic T lymphocyte-associated protein 4 (CTLA4) (2). CTLA-4 and PD-1 are present on the surface of T-cells and can inhibit their activation. CTLA-4 is present in regulatory T cells (Treg cells) and assists in immunological suppression. PD-1 is also present on the surface of B cells and other cells involved in immune response (3).

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When PD-1 interacts with its corresponding proteins, it can inhibit the T-cell response. Nevertheless, cancer cells present in the tumor microenvironment can evade the effects of anti-tumor mechanisms by activating these regulatory sites via the amplification of CTLA4 or PD-1/PD-L1 expression. In addition, they endeavor to do this via inhibiting antigen presentation (3).

The excessive expression of these checkpoints on the surface of immune cells may restrict the ability of the immune system to recognize and target cancer cells. This allows the cancer cells to evade examination and proliferate without restraint. It is a frequent occurrence in cancer cells and may serve as a mechanism for developing resistance to immunotherapy. Moreover, the immune system recognizes the distinct proteins or neoantigens produced by genetic changes in cancer cells as alien entities, making them potential targets for the immunological response to cancer (4). Nevertheless, there are instances when the immune system fails to accurately recognize neoantigens as alien, resulting in the cancer cells eluding immune monitoring and proliferating. This may happen when the immune system is weakened by checkpoint proteins, such as CTLA-4 and PD-1/PD-L1 (5). Checkpoint proteins restrict the activity of immune cells by anchoring certain ligands to the outer layer of cancer cells. This connection signals the immune cells to suppress their reaction, enabling the cancer cells to evade immunological assault. Immune checkpoint inhibitors (ICIs) enhance the effectiveness of the immune system in fighting cancer cells by inhibiting checkpoint proteins. Therefore, genetic changes in cancer cells may produce neoantigens that can be targeted for immune-mediated control of tumors (6). Nevertheless, the activity of the immune response could be restricted by checkpoint proteins. By inhibiting these checkpoint proteins with ICIs, it is possible to eradicate cancerous cells and enhance the effectiveness of immunotherapy. These medications may be used to target and inhibit the route of immunological checkpoints that are overexpressed, thus enhancing the ability of the immune system to detect and eliminate uncontrolled proliferating cells (6). This study specifically examines ICIs and their significance in the treatment of cancer. The origins of ICIs in immunotherapy may be traced back to the 1890s. However, its use for cancer treatment specifically began in the 1990s, when scientists first recognized the significance of immune checkpoints in controlling the immune response. The first ICIs for cancer therapy were created in the early 2000s, however, they were officially approved for treating skin cancer only around 2010 (7, 8). Since their introduction, ICIs have played a crucial role in the treatment of cancer and have had a remarkable effect on patient outcomes in several types of cancer, including melanoma, lung tumors, hepatic carcinoma, tumors of the head and neck, ovarian cancer, renal cell tumors, and others. These medications have resulted in enduring therapy responses and even complete remission in cancer patients with advanced-stage disease (9).

Introduction of ICIs

Immune checkpoints are categorized as immune cell surface receptors that regulate the activation or suppression of immunological responses. CPIs are a kind of immunotherapy that enhances the immune response against tumors by blocking the cell surface receptors of T cells (10). This category of immunotherapy has been extensively studied and is now regarded as the most fully researched. It plays a crucial part in the treatment of many types of cancer. Two very effective strategies for inhibiting checkpoints that have gained significant popularity in the last ten years are the blockage of PD-1/PD-L1 and CTLA-4 molecules. Additional targets, including inhibitory receptors such as T-cell immunoglobulin and mucin 3 (Tim-3), V-domain Ig suppressor of T-cell activation (VISTA), lymphocyte activation gene 3 (Lag-3), and activating molecules such as OX40 (CD134) and glucocorticoid-induced TNFR-related protein (GITR), are currently being studied. The identification of T-cell-negative regulation by CTLA-4 served as a catalyst for the adoption of CTLA-4 blockage as a kind of cancer immunotherapy (11). The first research conducted by Allison et al. has shown that inhibiting CTLA-4 in mice effectively halted tumor growth and facilitated the development of immunological memory, enabling the animals to consistently reject the tumor. Due to the positive results in preclinical models, humanized monoclonal antibodies have been developed to block the interaction between CTLA-4 and its ligand (B7) in cancer patients (12). This has led to the initiation of clinical studies. This marked the beginning of a significant change in the area of cancer immunotherapy since it effectively stimulated the immune system to target tumors. The finding by Honjo et al. that the interaction between PD-1 and PD-L1 leads to T-cell fatigue sparked the concept of targeting this process as a novel approach in cancer immunotherapy, warranting more exploration (13). Studies conducted in preclinical models have shown an increase in T-cell activation and interaction when PD-L1 inhibition is applied. Furthermore, the blocking of similar nature in mice tumor models demonstrated an increase in the immune response specific to the tumor cells and resulted in the regression of the tumor. The positive outcomes shown in preclinical research regarding PD-1/PD-L1 suppression have stimulated the creation of several

humanized antibodies and the initiation of clinical trials in individuals with advanced malignancies. The many classifications of these antibodies and their specific uses are further elaborated upon in the subsequent sections (13).

T cell CPIs

CTLA-4

CTLA-4 is a molecule that acts as an inhibitory checkpoint and is found in high levels on both activated T cells and Tregs. Dr. James Allison's groundbreaking preclinical research showed that CTLA-4, a molecule similar to CD28 but with a stronger binding to B7 ligands, effectively blocks T-cell proliferation and the generation of IL-2 by outperforming CD28 binding (14). CTLA-4 expression is triggered during T cell activation and limits the excessive growth of activated T cells. Significantly, the obstruction of CTLA-4 interaction by using an anti-CTLA-4 antibody to hinder the "switch-off signals" in T cells resulted in long-lasting T cell-mediated anti-tumor immune responses and tumor regression in mouse models (15). Following preclinical investigations, it was shown that the enhancement of tumor rejection caused by anti-CTLA-4 was due to an augmentation in effector CD4 and CD8 T cells, accompanied by a reduction in Tregs. Importantly, the effectiveness of anti-CTLA-4 treatment was not restricted to only one kind of tumor. Multiple studies done on various mouse tumor models showed that anti-CTLA-4 therapy had wide-ranging effectiveness. The effectiveness of ipilimumab, a human monoclonal anti-CTLA-4 antibody, was evaluated in clinical studies. The results demonstrated significant clinical effectiveness, leading to its approval by the Food and Drug Administration (FDA) for the treatment of melanoma in 2011 (16). Significantly, a cohort of patients diagnosed with advanced melanoma who had this treatment exhibited enduring clinical responses and experienced long-term survival advantages that persisted for a period of up to 10 years. The clinical endorsement of ipilimumab has paved the way for a kind of cancer immunotherapy known as ICT. Since then, the discipline of Information and Communication Technology (ICT) has made significant advancements by providing long-lasting therapeutic advantages, such as curing patients with different kinds of solid malignancies, and has resulted in many approvals from the FDA (17).

Programmed Death 1 (PD-1)

PD-1 is a T cell inhibitory checkpoint molecule that acts as a checkpoint in T cells. Its role as a checkpoint molecule was understood with the identification of its ligands, programmed death ligand 1 (PD-L1) and PD-L2. Experiments conducted using Pd1−/− mice demonstrated that the interaction between PD-1 and its ligands is responsible for preserving T-cell tolerance in the peripheral regions. PD-1 binding prevents TCR signaling by attracting the Src homology 2 domain-containing protein tyrosine phosphatase 1 (SHP-1) and 2 (SHP-2) tyrosine phosphatases, which remove phosphate groups from molecules implicated in TCR signaling, such as CD3ε and ZAP-70 (18). PD-1 is abundantly present in T cells that have infiltrated tumors, particularly in T cells that are tired. Tumor cells and other kinds of cells inside the tumor, such as endothelial cells, epithelial cells, and myeloid cells, express PD-L1. On the other hand, PD-L2 is mostly expressed by antigen-presenting cells (APCs). Preclinical investigations have shown that the binding of PD-1 to PD-L1 in the tumor microenvironment (TME) hinders the ability of T cells to respond against tumors. On the other hand, blocking this relationship using anti-PD-1/PD-L1 antibodies enhanced the immune response of T cells against tumors, resulting in the shrinkage of tumors in several mouse tumor models (19). Anti-PD-1 and anti-PD-L1 antibodies have been shown effective in clinical trials for several kinds of tumors, including melanoma, tumors of the kidney (RCC), and non-small cell lung cancer (NSCLC). In 2014, the FDA granted first approval for the use of monoclonal anti-PD-1 antibodies to treat patients with metastatic melanoma. Subsequently, the FDA authorized additional immune checkpoint medications that target the PD-1/PD-L1 pathway for treating various kinds of tumors (20).

Pembrolizumab, a humanized IgG4 monoclonal antibody, was first authorized by the FDA for the treatment of metastatic melanoma and NSCLC. Over the following years, the treatment received approval for various types of tumors, such as squamous cell carcinoma of the head and neck (HNSCC), solid tumors with high microsatellite instability (MSI-H), progressed gastric cancer, cervical cancer, urothelial tumors, triple-negative breast cancer (TNBC), and tumors with the high mutational burden (TMB-H). The FDA has approved for pembrolizumab to be used in the treatment of advanced endometrial cancer that is MSI-H or mismatch repair-deficient (dMMR), based on the findings of the KEYNOTE-158 study (21).

Nivolumab, a completely human IgG4 monoclonal antibody, received FDA approval in 2014 for the treatment of melanoma. As a result, new uses were authorized for the treatment of NSCLC, renal cell carcinoma, Hodgkin's lymphoma, head and neck squamous cell carcinoma (HNSCC), hepatocellular carcinoma, esophageal squamous cell carcinoma, pleural mesothelioma, and colorectal cancer (CRC) with deficient mismatch repair (dMMR) or high microsatellite instability (MSI-H) (22). In 2022, nivolumab received many successful approvals from

the FDA for several indications. The combination of Nivolumab and LAG-3 inhibitor has received approval for treating unresectable or metastatic melanoma, after the findings of the RELATIVITY-047 study. Furthermore, the combination of nivolumab and chemotherapy has been authorized as neoadjuvant treatment for early-stage NSCLC based on the findings of the CheckMate-816 trial (23). In addition, nivolumab has been granted permission for its use in conjunction with either chemotherapy or ipilimumab for patients diagnosed with unresectable advanced or metastatic esophageal squamous cell carcinoma (ESCC), as indicated by the CheckMate-648 study (24).

PD-L1 Inhibitors

PD-1 can inhibit activated immune cells by interacting with its ligands, PD-L1 and PD-L2. PD-L1, often referred to as B7-H1, is extensively expressed in many kinds of tumors and immune cells, whereas PD-L2 is mostly found in normal dendritic cells. Tumors may manipulate the PD-1/PD-L1 pathway to weaken the immune response mediated by T-cells, resulting in the excessive growth of cancer cells. The comprehension of this interplay has become PD-L1 a compelling target for immunotherapy. Three PD-L1 inhibitors have been authorized by the FDA: atezolizumab, durvalumab, and avelumab (25, 26).

Atezolizumab, a humanized IgG1 anti-PD-L1 monoclonal antibody, received approval in 2016 for the treatment of urothelial cancer (27). As a result of the higher incidence of response, the diagnosis was subsequently extended to include NSCLC, SCLC, melanoma, and hepatic carcinoma. It is worth mentioning that the therapy was previously recommended for TNBC (triple-negative breast cancer), but it is no longer accessible as a therapeutic choice due to the failure to achieve the desired outcome in the IMpassion130 clinical study (28, 29). Durvalumab is a monoclonal antibody of the IgG1 class that specifically targets PD-L1 and was first authorized by the FDA for the therapeutic management of urothelial bladder cancer (30). After one year, the medication received approval for the treatment of stage III NSCLC and extensive stage SCLC (31). The FDA approved the use of durvalumab in conjunction with chemotherapy for patients diagnosed with biliary tract cancer (BTC) in 2022. This decision was made after the evaluation of the TOPAZ-1 clinical study (32). Avelumab, a completely human IgG1 anti-PD-L1 monoclonal antibody, received FDA approval in 2017. It was a significant advancement since it became the first therapy for metastatic Merkel cell carcinoma (MCC), a rare but aggressive kind of skin cancer (33). Subsequently, the therapy received approval for individuals diagnosed with urothelial carcinoma and renal cell carcinoma. Significant progress has been made in the development of novel CPIs for various indications (34).

Despite the rapid progress of CPIs as a kind of immunotherapy, their effectiveness might be hindered by many hurdles and limitations. Primary resistance, which refers to the tumor's lack of response to the first therapy, may occur in the context of CPI treatment. Furthermore, there might arise issues associated with acquired resistance, whereby the previously administered medicine becomes ineffective (35). Observations have been made in individuals with melanoma, indicating that around 30% initially exhibit a favorable response to treatment, but subsequently develop acquired resistance throughout the course of therapy. Another significant constraint in the use of CPIs is the emergence of immune-related adverse events (irAEs). This particular kind of undesirable incident may happen either at the beginning or later on in the course of the treatment regimen, and it presents itself in various ranges and levels. Moreover, other biological elements might directly or indirectly improve or restrict the CPI's performance, which will be further elaborated in the subsequent sections (35).

Additional immune regulatory molecules

Aside from CTLA-4 and PD-1, several additional immune regulatory molecules with positive and negative effects have been discovered and studied recently as possible targets for ICT. LAG-3 is abundantly present in activated T cells. It interacts with MHC class II, galectin-3, and α-synuclein. LAG-3 has immunosuppressive properties as it enhances the activity of Tregs and inhibits the function of T cells that carry out immune responses. LAG-3 specifically identifies stable MHC II: peptide complexes and triggers inhibitory signals via its intracellular domains upon attaching to them (36). Recent research has shown that the cytoplasmic tail of LAG-3 induces the separation of the tyrosine kinase, Lck, from CD4/CD8 co-receptors, resulting in a disruption of TCR signaling and the deactivation of T cells. Crucially, the injection of anti-LAG-3 antibody enhances the immune response of T cells against tumors in preclinical models (37). T cell immunoglobulin and mucin-domain containing-3 (TIM-3) is a molecule that acts as an inhibitory immunological checkpoint and is found in high levels on T cells that are malfunctioning or fatigued. TIM-3 interacts with galectin-9, high-mobility group protein B1, phosphatidyl serine, and carcinoembryonic antigen cell adhesion molecules by binding. 1 Significantly, the simultaneous targeting of the TIM-3 and PD-1 pathways has shown exceptional effectiveness in preclinical models of solid malignancies (38).

Unlike inhibitory checkpoint molecules, co-stimulatory molecules present in T cells enhance T cell-mediated anti-tumor immune responses. ICOS is a chemical that boosts the effectiveness of T lymphocytes by enhancing their effector activities. Furthermore, T cell effector activity is further enhanced by some members of the tumor necrosis factor (TNF) receptor family, such as glucocorticoid-induced TNFR-related gene (GITR), OX40, and 4-1BB, which serve as co-stimulators (39).

Primed T cells have a high level of expression of 4-1BB. Engaging 4-1BB with its ligand 4-1BBL increases the production of genes that prevent cell death in T cells, hence improving the long-lasting memory responses of cytotoxic T cells (39). Overexpression of 4-1BBL and the use of agonistic monoclonal antibodies that target 4-1BB enhanced the immune response of CD8 T cells against tumors and resulted in the rejection of tumors in preclinical models (39).

OX-40 is a co-stimulatory receptor that is expressed on T lymphocytes temporarily after they are activated (40). Activation of OX-40 by OX-40L improves the longevity of T cells and promotes the development of long-term memory. Furthermore, it hinders the activity of Tregs and the formation of induced Tregs. Significantly, increased levels of OX-40L and the use of agonistic anti-OX40 antibodies resulted in the greater rejection of tumors in several mouse models (40).

Diagnostic indicators of ICI-based immunotherapy

Several biomarkers, including PD-L1 expression, tumour mutation burden (TMB), microsatellite instability, microbiota, hypoxia, interferon-gamma (IFN-γ), and extracellular matrix, have been identified as potential factors that might enhance the reaction to immunotherapy for individuals receiving ICIs (41).

PD-L1 expression

PD-1 is a signaling receptor that is present on the outer surface of T cells. PD-1 and its ligand, programmed cell death PD-L1, have been extensively investigated in clinical trials as biomarkers for immunotherapy based on ICIs (4). The presence of PD-L1 was shown to be elevated by inflammatory agents, namely interferon-γ, in the TME. PD-L1 expression was also shown to hinder the protective function of CTLs and decrease the occurrence of persistent viral infections (42). Pathologists evaluate and quantify the PD-L1 expression using immunohistochemistry (IHC). One possible approach to enhance the immune system's ability to combat tumor cells is to target the PD-1/PD-L1 connection using monoclonal antibodies (mAbs) (43). This may lead to the suppression of this interaction. Research done by Bellmunt et al. assessed 542 individuals with advanced urothelial carcinoma and determined that Pembrolizumab had improved survival outcomes and fewer adverse effects compared to treatment (44). The KEYNOTE-522 trial conducted a comparison between patients who were administered Pembrolizumab plus chemotherapy and patients who were given placebo and chemotherapy. The study revealed that the former group had superior pathological results (45). The KEYNOTE-024 trial demonstrated that administering a fixed dosage of Pembrolizumab (200 mg) resulted in increased overall survival (OS) and progression-free survival (PFS), as well as reduced treatment-related side events, in NSCLC patients with a PD-L1 tumor percentage score (TPS) of 50% or higher, compared to chemotherapy (45). Moreover, the findings of the KEYNOTE-048 study indicated that Pembrolizumab enhanced overall survival (OS) in patients with recurrent or metastatic head and neck squamous cell carcinoma (R/M HNSCC) as the expression of PD-L1 increased (46). This highlights the significance of PD-L1 expression as an indicator of responsiveness to ICIs. The findings from CHECKMATE 040 have led to the approval of the combined medication of Nivolumab and Ipilimumab as a second-line treatment for HCC in patients who are already undergoing sorafenib (47).

Tumor mutation burden

Tumor mutational burden (TMB) refers to the number of mutations (muts) per megabase (Mb) in cancer cells. The threshold for TMB to be classified as high varies depending on the kind of tumor (thresholds of 10, 20, and >30 muts/Mb have been used in various studies). High tumor mutational burden (TMB-H) has been used as a promising biomarker to predict a substantial response to CPIs (48). A 2015 trial demonstrated a significant improvement in the objective response rate (ORR) and progression-free survival (PFS) among NSCLC patients with high tumor mutational burden (TMB-H) when treated with pembrolizumab. A separate trial demonstrated a strong correlation between the combination of nivolumab and ipilimumab and extended progression-free survival (PFS) in NSCLC patients with TMB-H. Furthermore, this positive response was sustained regardless of the absence of PD-L1 expression (49).

Furthermore, the KEYNOTE-158 research, which primarily focused on around 10 types of cancer (predominantly solid tumors), has shown a substantial treatment response in patients with TMB-H when treated with pembrolizumab. As a reaction, the FDA has approved for the use of the same medication in treating all solid tumors with a TMB-H of 10 or more mutations per megabase (50). Although both PD-L1 expression and TMB are used as biomarkers

to determine the effectiveness of CPIs, they do not exhibit a significant correlation in the majority of cancer types. Furthermore, they seem to function via separate processes to govern the response. While some data is suggesting that TMB may be a more reliable indicator of how well a patient would respond to CPIs compared to PD-L1 expression, the overall effectiveness of TMB in all types of solid tumors is uncertain and requires more research. For instance, individuals with glioma who have a low tumor mutational burden (TMB-L) but not a TMB-H have shown a positive response to CPIs. Although TMB has achieved a noteworthy achievement in predicting response to CPIs, there is still a need for a more dependable and all-encompassing biomarker(s) that has not been fulfilled (51).

Microbiota

The human body harbors microbiota in several regions, with notable concentrations in the skin, saliva, and gastrointestinal tract. The microbiome has the ability to impact ICIs treatment by modulating the immune system (52). A research conducted in live mice with CT26 tumors shown that a high level of microbial diversity may significantly enhance the response to ICIs by boosting the release of IL-2 and IFN- compared to animals treated with antibiotics (53). Consequently, there is a proposal suggesting that the microbiome can improve the immune response, trigger inflammation, or disturb the equilibrium between cell growth and cell death, ultimately leading to an increase in tumor formation (53). According to reports, the gut microbiota triggers T cell-mediated responses, leading to the specific attack on tumor cells. In addition, melanoma patients who received anti-PD-L1 treatment had elevated levels of *Bifdobacterium longum*, *Collinsella aerofaciens*, and *Enterococcus faecium*, underscoring the significance of the microbiome (54). Zheng et al. recently published a study documenting dynamic changes in the gut microbiota of patients with HCC undergoing immunotherapy. Furthermore, the metagenomic sequencing data revealed a greater abundance of higher taxa in the fecal samples of patients who responded to immunotherapy, as opposed to those who did not react. This emphasizes the significance of the microbiome in controlling immune responses (55).

Extracellular matrix

The extracellular matrix (ECM) is a complex structure made up of large molecules outside of cells that offer biochemical assistance for tissues. Desmoplasia, also known as the proliferation of connective tissue, has been associated with a worse prognosis in patients with solid tumors (56). This is because there is a significant increase in collagen and fibroblast infiltration inside the TME. Stiffness is the main differentiating factor between normal and malignant ECM. Metalloproteases (MMPs) have the ability to degrade components of the ECM and produce smaller fragments of large molecules (57). These fragments may exhibit either pro- or anti-tumorigenic effects in certain forms of cancer. Consequently, fragments generated from collagen IV, such as tetrastatin, canstatin, and tumstatin, can decrease the invasiveness and proliferative characteristics of tumor cells by attaching to integrins (α3β1, α5β1, or αVβ3). In addition, Lysyl oxidase (LOX) hinders the movement of T cells to ECM and dampens the immunological response. The KPC model was employed to illustrate that the inhibition of LOX may enhance the infiltration of T cells, thereby leading to improved reaction rates to immunotherapy based on ICIs (58, 59).

New formulations of immune checkpoint inhibitors

Combining immune checkpoint drugs with chemotherapy

Clinical studies are now evaluating many combinations of ICT and chemotherapy regimens for the treatment of different types of malignancies. The phase III CheckMate 648 study, which included 970 patients with advanced, recurring, or metastatic esophageal squamous cell carcinoma, demonstrated that the combination of nivolumab with chemotherapy treatment resulted in a substantial improvement in OS as compared to chemotherapy alone (60). Moreover, clinical studies that have administered the combination of immunotherapy and chemotherapy to patients with NSCLC have shown a noteworthy increase in survival rates. The findings of the CheckMate 816 trial, which focused on patients with resectable NSCLC, demonstrated that the addition of neoadjuvant nivolumab alongside platinum-based chemotherapy resulted in enhanced event-free survival and a higher rate of pathological complete response. Specifically, 24% of patients in the combination group achieved a pathological complete response, compared to only 2.2% of patients who received chemotherapy alone (24).

These results provide a compelling justification to utilize this combination as the first therapy choice for individuals with advanced NSCLC. Furthermore, the use of carboplatin and etoposide in conjunction with anti-PD-L1 (atezolizumab) led to a notable enhancement in the median OS duration, increasing from 10.3 months (in the placebo group) to 12.3 months in the treatment group. This positive outcome prompted the FDA to approve the combination as the first treatment option for small cell lung cancer (SCLC) (61). It is important to mention that atezolizumab was granted rapid authorization by the FDA as an initial treatment for individuals with metastatic urothelial carcinoma, according to the findings of the IMvigor210 trial. However, recently

released findings from the phase III IMvigor130 trial (NCT02807636) demonstrated that the combination of atezolizumab and chemotherapy did not enhance overall survival when compared to chemotherapy alone. Further assessment is needed to evaluate the immunosuppressive influence of chemotherapy, taking into account factors such as dosage and timing. This evaluation should be conducted in appropriate preclinical studies that focus on particular tumor types, to enhance the effectiveness of combining chemotherapy with immunotherapy (62).

Immunological checkpoint inhibitors and radiation

Immuno-oncologic methods have the potential to improve radiation therapy in cancer treatment, and vice versa. Radiotherapy has a double impact on the tumor cells. It not only directly impacts the tumor cells but also modifies the immune environment in the TME (63). This is achieved by releasing tumor antigens, triggering a type I interferon (IFN) response, and enhancing the infiltration of effector CD8 T cells. Regrettably, the clinical studies including patients with metastatic NSCLC, metastatic head and neck squamous cell carcinoma, and Merkel cell carcinoma did not demonstrate any therapeutic effectiveness when radiation was combined with immune checkpoint inhibition. Nevertheless, significant pathological reactions showed up among individuals with early-stage NSCLC when stereotactic body radiotherapy was combined with neoadjuvant durvalumab. This indicates that the effectiveness of radiation when combined with immune checkpoint inhibition may vary depending on the stage of the illness and the timing of therapy (64, 65).

Immune checkpoint inhibitors with oncolytic viruses

Utilizing various methods, such as oncolytic viruses (OVs), to enhance the immune response has become increasingly popular. OVs offer a distinct advantage by specifically targeting cancer cells, replicating within them, and causing their destruction. This process also leads to the release of tumor-specific antigens, which trigger IFN signaling and create an inflammatory TME (66). Currently, there is just one medication called talimogene laherparepvec (T-VEC) that has been licensed by the FDA to treat the symptoms of individuals with advanced melanoma. T-VEC is a therapy that utilizes the herpes simplex virus 1 (HSV-1). The Phase 1b research, which combined T-VEC with anti-CTLA4 in incurable melanoma, demonstrated a substantial improvement in overall response rate (ORR) compared to ipilimumab alone. The ORR was 39% with the combination therapy, whereas it was only 18% with ipilimumab alone. The responses were observed in both the injected skin and visceral lesions (67).

Nevertheless, the recent phase 3 MASTERKEY-265 research, which had a larger sample size, compared the efficacy of T-VEC with pembrolizumab as a single agent. The study revealed an enhanced overall response rate (48.6% vs. 41.3%). However, it failed to achieve its main objectives of progression-free survival (PFS) and OS. Thorough correlation analyses of the tissues are necessary to evaluate how OVs affect immune modulation, the impact of long-term interferon stimulation, the selection of ICT, and the design of the clinical trial. These factors are crucial in comprehending the underlying causes for the absence of survival advantages, despite observed responses with this logical combination (68).

Combining immune checkpoint inhibitors with operation

The administration of systemic treatments to attain pathological reactions and enable the operation is well-recognized in several kinds of tumors, such as the application of neoadjuvant chemotherapy for the management of breast cancer or urothelial carcinoma. Moreover, the neoadjuvant condition enables the analysis of the whole tumor specimen, which offers enough tissue for comprehensive immune surveillance to determine the fundamental causes of both treatment response and resistance. During our presurgical clinical study of ipilimumab in individuals with bladder cancer, we observed the presence of ICOShiCD4 T cells in tumor tissues and later in the bloodstream. This finding establishes ICOShiCD4 T cells as a pharmacodynamic marker for anti-CTLA-4 treatment (69). Further investigations have verified the practical significance of the ICOS/ICOSL pathway in reaction to anti-CTLA-4 treatment, which supports the idea of combining therapies (69).

Neoadjuvant ICT has shown encouraging efficacy in several kinds of tumors, such as high-risk, human epidermal growth factor receptor 2 (HER2)-positive early breast cancer, non-small cell lung cancer, and muscle-invasive bladder cancer. Research indicates that the timing of information and communication technology (ICT) about surgery has an impact on the body's reactions. In mouse models of spontaneously breast cancer metastasis, neoadjuvant anti-PD-1 treatment significantly decreased the spread of cancer to other parts of the body (70). This effect was not seen with adjuvant immunotherapy, which suggests that the prolonged reaction of tumor-specific CD8 T cells may be responsible for the reduction in metastases. This response may be linked to the discharge of tumor antigens caused by surgery. However, ICT has shown advantages in the adjuvant treatment of some kinds of tumors, including melanoma and NSCLC. However, there is inconsistent evidence about its effectiveness in other tumor types, like renal cancer (71).

Immune-related toxic reactions to ICIs

The immunological response to ICIs exhibits

variability, distinct from the response seen with conventional chemotherapy. A multitude of folks encounter adverse consequences, including weariness, dermatological eruptions, and colitis (inflammation of the colon). Certain individuals may encounter a strong response, known as an immune-related adverse event (irAE) (72). irAEs may have a profound influence on several organs, including the gastrointestinal system, skin, liver, endocrine glands, myocarditis, and others. The incidence of adverse events resulting from irAEs caused by ICIs varies depending on the particular medication and the individual patient's health profile. The predicted fatality rate associated with these medicines ranges from 0.3% to 1.3%. Severe or negative side effects from immunotherapy medications often manifest early in the course of treatment and may be significant (73). Nevertheless, the risk associated with this treatment is relatively reduced in comparison to other medical interventions like as chemotherapy or stem cell transplantation. The kind of adverse effects may also differ depending on the specific mix of medications used. Colon inflammation-related mortality is more prevalent among patients undergoing treatment with anti-CTLA-4 medications, while mortality due to lung inflammation is more common in individuals getting anti-PD-1 or anti-PD-L1 therapies (73).

Adverse events (irAEs) resulting from the delivery of anti-CTLA-4 antibodies occur in sixty percent of patients who receive treatment and might vary in severity. Out of them, a significant proportion of ten to thirty percent of individuals encounter severe (grade 3-4) irAEs. The incidence of irAEs is directly proportional to the dosage, meaning that larger dosages are more likely to result in a greater occurrence of negative side effects. The majority of grade ≥ 3 irAEs occur within 8-12 weeks after starting the medication. The occurrence of skin rash occurs earliest, whereas diarrhea and/or colitis are the most common irAEs resulting from the delivery of anti-CTLA-4 antibodies. Additional toxicities include endocrinopathies, hepatotoxicity, and infrequent toxicities like neuropathies, autoimmune thrombocytopenia, and syndromes resembling Stevens-Johnson syndrome. Neurological irAEs manifest in 3.8% of patients receiving anti-CTLA-4 antibodies, with serious side effects of grade ≥ 3 occurring in fewer than 1% of individuals (74).

Anti-PD-1 antibodies had a lower occurrence of irAEs compared to anti-CTLA-4 antibodies. The majority of Anti-PD-1-related irAEs occur during the first 6 months after initiating medication treatment. Typical side effects (seen by fewer than 25% of patients) include skin rash, tiredness, joint pain, headache, itching, diarrhea, inflammation of the colon, inflammation of the lungs, liver inflammation, and hormonal disorders. The incidence of grade ≥ 3 irAEs is around 10% in patients treated with anti-PD-1 medicines, however, it may reach up to 30% in patients treated with anti-CTLA-4 antibodies. Neurological irAEs manifest in around 2.9% of patients who undergo anti-PD1 medication (75). Nevertheless, the occurrence of cutaneous, hepatic, and pulmonary-related irAEs is more common when administering anti-PD1 antibodies compared to anti-CTLA4 antibodies. Conversely, thyroid and lower digestive tract irAEs, such as colitis, are more prevalent with anti-CTLA4 antibody administration. There is a suggestion that tailored immunosuppression, using anti-PD-1 antibodies together with antibodies that target specific inflammatory mediators, might prevent the worsening of autoimmune illnesses. This can be done without affecting the effectiveness of anti-PD-1 medications. In the event of irAEs, one might consider attempting the management, monitoring, and withdrawal of the medicines (75).

Outlook and conclusion

ICIs, or immune checkpoint inhibitors, function in collaboration with the immune system and represent a significant advancement in the field of cancer therapy. They assist in bolstering and intensifying the body's innate immunological response to cancer, resulting in an enhanced anti-tumor reaction. These medications have completely transformed the approach to cancer treatment, and they possess the capacity to further influence patient outcomes substantially in the future. Nevertheless, similar to other cancer therapies, ICIs may result in adverse effects, including immune-related adverse events (irAEs) such colitis, hepatitis, and dermatological responses. These adverse effects may often be controlled with timely identification and intervention. The potential of ICIs in cancer therapy is very promising for the future (76).

Nevertheless, despite the notable efficacy of ICIs in cancer treatment, there are instances when their effectiveness may be limited or malignancies may develop resistance to ICIs, necessitating the use of alternate therapeutic strategies. This encompasses tumors characterized by a low TMB, low expression of PD-L1, an immunosuppressive tumor microenvironment, or alternate mechanisms of immune evasion. Cancers characterized by a low TMB, such as particular forms of breast and prostate cancers, may lack a sufficient number of neoantigens (antigens resulting from tumor-specific mutations) to elicit a strong immune response. Similarly, tumors with low expression of PD-L1 are not effectively responsive to PD-1/PD-L1 inhibitors. The presence of regulatory T cells, myeloid-derived suppressor cells, and other immune-suppressive components in tumors with an immunosuppressive microenvironment hampers the efficacy of ICIs (77).

Targeted, combined, adoptive, or vaccine-based

therapy may be beneficial in such instances. The combination of ICIs with other treatments, including chemotherapy, radiation, specific treatments, or other immunotherapies, might potentially improve the overall therapeutic response. It can additionally involve focusing on a pair or group of ICIs. The concurrent use of ICIs with numerous therapeutic agents is a very active area of research and clinical advancement in the area of cancer immunotherapy. The objective is to combine several methods of action, amplify the total immune response against tumors to combat resistance and increase the results for patients. This has been well evaluated elsewhere (78).

This study primarily examined CTLA-4, PD-1, and PD-L1, but it also identified other potential targets for ICIs that show promise. Some examples of these are LAG-3, TTIM-3, TTIGIT, VVISTA, and B7-H3 inducible T cell costimulatory (ICOS) (79). Clinical studies are being conducted to test inhibitors that target these receptors. However, the effectiveness of these inhibitors may change depending on the specific kind of cancer and the characteristics of the patients. Therefore, it is crucial to conduct thorough clinical trials to evaluate the safety and effectiveness of these inhibitors (78).

In the future, research on ICIs is anticipated to progress further, resulting in the creation of immunotherapies that are both more efficient and safer. Future research is expected to concentrate on novel inhibitor development, combination treatment, and exploration of unexplored malignancies. In addition, the efficacy of ICIs might differ across patients, and scientists are investigating methods to distinguish individuals who react positively to ICIs from those who do not. This might potentially result in the advancement of individualized medical strategies, whereby patients are administered the most probable medication to yield positive outcomes for them. Furthermore, the identification of biomarkers that may accurately predict the response to these medicines has the potential to inform treatment choices and ultimately improve patient outcomes.

Authors' Contribution

Akram Sadat Ahmadi and Atefeh Valaei were involved in the conceptualization, design and writing of the manuscript draft. The authors read and confirmed the final manuscript.

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Conflicts of Interest

The authors declare no conflict of interest.

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