Immune Checkpoint Inhibitors Combined with Chemotherapy in The Treatment of Lung Cancer

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Abstract. Immune checkpoint inhibitor (ICI) therapy is the most commonly used immunotherapy regimen. The clinical application of this medicine has been authorized for the treatment of several neoplasms such as melanoma, renal, head and neck, bladder, etc. Lung cancer treatment has witnessed significant advancements, positioning it as a pivotal component within the broader framework of comprehensive lung cancer management. However, due to the heterogeneity of tumors and the intricacy of the microenvironment of tumors, the effective rate of ICIs alone is low in non-selected patients. Surgery, chemotherapy, radiotherapy, targeted therapy, and other treatments can have synergistic effects with immunotherapy, and combination therapy has become a hotspot for exploration. This article centers on the research advancements in the therapeutic approach of combining immune checkpoint inhibitors (ICIs) with chemotherapy. This text offers an introductory overview of the distinct mechanisms of action associated with these two treatment modalities, highlighting the significance of their combined use in the context of lung cancer treatment. The objective is to offer a reference point for future clinical treatments of lung cancer.

Keywords: Immune checkpoint inhibitor; immunotherapy; Lung Cancer.

1. Introduction

Lung cancer is a significant disease endangering human health, and its incidence and mortality rates are the highest among human beings. Human research on lung cancer has been quite in-depth, and many treatment programs have been developed, with conventional treatments including chemotherapy, targeted therapy, and so on. However, these treatment options still have many limitations. Chemotherapy is the most traditional treatment option, mainly using drugs to kill cancer cells or inhibit their growth. However, the side effects of chemotherapy on the body are hard to ignore, especially the negative impact on the immune system, which kills the cancer cells in the body and damages normal cells. Sometimes, chemotherapy can also lead to genetic mutations in tumors, making them resistant to treatment.

Compared to chemotherapy, ICIs, as an emerging immunotherapy, are one of the most talked about tumor immunotherapies. ICIs mainly work on the human immune system to enhance the body's resistance to tumors by the suppression of signaling pathways such as PD-1, CTLA-4, etc. Single-agent therapy with ICIs has achieved good results in many patients and has been approved as a first-line drug for various tumor treatments. However, single-agent ICIs have the drawbacks of limited efficacy and susceptibility to drug resistance. Therefore, developing combination therapeutic strategies to improve the effectiveness of ICIs has become a research hotspot in the field of antitumor. Hence, the present study centers on the examination of fusion therapies involving chemotherapy and ICIs to elucidate the synergistic mechanism resulting from the combination of these two medications. The analysis encompasses an exploration of the respective agents and the existing research advancements, with a particular emphasis on their application in the management of NSCLC.

2. ICIs and Chemotherapy

2.1. Mechanism of actions and types of ICIs

The term "immune checkpoints" pertains to a group of molecules and signaling pathways that are primarily situated on the external membrane of immune cells. Under normal conditions,

immunological checkpoints perform a crucial function in regulating the activation of immune cells by exerting a suppressive effect.

Cancer cells employ a strategy to elude the immune response by generating inhibitory signaling molecules that dampen the functionality of immune cells. These inhibitory molecules include immunosuppressive molecules like PD-L1 and inhibitory cytokines such as TGF-β. IL-10 is one of these inhibitory cytokines, and the receptor for it is the IL-10R, which is expressed on the surface of the immune cell. When IL-10 binds to the IL-10R, it can activate signaling pathways downstream of IL-10R cells. Janus protein kinase (JAK) and STAT are the most important intracellular signaling pathways. By interacting with its receptor, IL-10 activates the JAK1/Tyl2 signaling pathway, which phosphorylates STAT3 and localizes it in the nucleus as a dimer, regulating the expression of the target genes and thus controlling the organism's immune response [1].

ICIs are a type of immunotherapy based on inhibiting immune checkpoints and different kinds of ICIs can act on many types of immune checkpoints.

2.1.1 PD-1 pathway

Two PD-1 ligands, PD-L1, and PD-L2, are often seen in tumor cells. among others, immune cells. Typically, T-lymphocyte activation is mediated by the TCR and occurs when antigens are recognized and then bind to MHC molecules produced on antigen-presenting cells. But when PD-1 binds to its ligand, TCR signaling is suppressed, which prevents T cells from being stimulated and from proliferating. The main function of PD-1 is to control T-cell proliferative responses to inflammatory responses brought on by infection in the surrounding tissues, with the secondary goal of lowering the risk of autoimmunity [2].

In addition, the combined action of these two ligands can also lead to insensitivity of T cells to antigens and failure to generate a robust immune response even when antigens stimulate T cells.

Certain tumors or pathogenic infections can inhibit tumor-specific T-cell activity by increasing PD-L1 expression on the tumor surface, leading to diminished immunocyte effects. Therefore, an inhibitor is needed to suppress the association involving PD-1 and its corresponding ligand. Currently, pembrolizumab, nivolumab, cemiplimab, and toripalimab are the main drugs approved for marketing by the FDA, of which the first ones, pembrolizumab and nivolumab, are monoclonal antibodies targeting PD-1. Clinical trials have shown that both drugs can be used to treat advanced melanoma and metastatic NSCLC, with objective remission rates of 25-40% in the treatment of melanoma. In addition, the drug has a longer effectiveness duration than standard chemotherapy [3].

2.1.2 CTLA-4 pathway

The cytokine receptor CTLA-4 is essential for negative regulation. T cell activation and proliferation are aided when CD28 attaches to B7 molecules in response to antigen-stimulated T cells. The B7 molecules (CD80, CD86) on the surface of APCs are uniquely recognized by CTLA-4, like CD28, however CTLA-4 functions in the opposite way from CD28. Once the immune response reaches a certain level, the expression of CTLA-4 is upregulated to prevent excessive immune response. CTLA-4 has a strong affinity for B7, which can inhibit the binding of CTLA-4 to B7 through competition and then inhibit the activation and proliferation of T lymphocytes [4]. Therefore, inhibiting CTLA-4 to achieve immunotherapy has become a direction worthy of in-depth research.

Ipilimumab, a monoclonal antibody, is widely utilized as the primary inhibitor of CTLA-4. Ipilimumab operates through targeted binding to the CTLA-4, thereby, the connection involving CTLA-4 and its corresponding B7 molecule is impeded. By suppressing the suppressive influence of CTLA-4 on T-cell activation, it is feasible to prevent this phenomenon.

A clinical experiment was conducted to assess the effectiveness and safety of Ipilimumab in combination with gp100 compared to Ipilimumab or gp100 alone. The study included a total of 676 patients diagnosed with stage III or IV melanoma and had the HLA A*0201 positive status. The participants were categorized into three distinct cohorts and thereafter allocated at random to one of three therapeutic protocols: a combination of Ipilimumab and gp100 (403 participants), Ipilimumab as a standalone treatment (137 participants), or gp100 as a standalone treatment (136 participants).

Results from this phase of the trial indicate that patients who received Ipilimumab and gp100 in combination had a median overall survival time of 10.0 months. Individuals who received simply gp100, on the other hand, had an average total survival time of 6.4 months. The observed survival time for patients receiving Ipilimumab alone was shown to be 10.1 months. Ipilimumab has significantly improved overall patient survival when added to the melanoma therapy regimen [5].

2.2. Fundamentals of Chemotherapy

In contrast to ICIs, chemotherapy does not target the organism itself but the tumor. Chemotherapy drugs usually cure or relieve cancer by killing cancer cells or inhibiting their growth.

One of the significant types of chemotherapeutic drugs used against lung cancer is Cisplatin, a platinum compound that inhibits the growth of cancer cells. When Cisplatin is used, the drug enters the cancer cell and binds to two neighboring guanine (G) residues in the DNA, forming a DNA-platinum complex. When Cisplatin binds to DNA, it forms crosslinks in the DNA strand, which makes it difficult for the strand to break and for the enzyme to secure correctly. This ultimately hinders the process of DNA replication. In addition to this, Cisplatin also interferes with the transcription process by blocking the binding of RNA polymerase. These interferences ultimately lead to the self-destruction of the cancer cell. When DNA is damaged or mismatched, it initiates intracellular communication, which leads to stress responses. The reactions encompass several mechanisms, such as cell cycle arrest for DNA repair, activation pathways, and apoptosis. Apoptosis is a cellular process that serves as a safeguard against the uncontrolled proliferation and metastasis of malignant cells by selectively eliminating cells that have incurred irreparable damage.

In the PARAMOUNT study trial, the researchers administered a combination of Cisplatin and the administration of pemetrexed was conducted on a cohort of individuals who had been diagnosed with advanced non-squamous NSCLC. In a subsequent trial, one group of patients continued to use Cisplatin and ALIMTA, while the other group received Cisplatin plus placebo plus ALIMTA—optimal supportive therapy. The results showed, in part, that survival was more favorable in patients who continued Cisplatin and ALIMTA. The findings of this study indicate that maintenance therapy techniques may have a beneficial impact on the management of advanced non-squamous NSCLC in patients who meet the eligibility criteria [6].

3. Immunotherapy in conjunction with chemotherapy has been utilized in the management of NSCLC

NSCLC is the prevailing variant of lung cancer. Adenocarcinoma is the primary histological subtype of NSCLC, accounting for around 40-50% of all cases. Besides tobacco smoking, other genetic mutations contribute to the heightened susceptibility to lung adenocarcinoma. Notably, mutations in the EGFR gene and the occurrence of heterologous tyrosine kinase (ALK) gene fusions have been identified as significant determinants. Squamous cell NSCLC is another subtype of NSCLC. Unlike other NSCLCs (e.g., adenocarcinoma), the tumor cells in SCC-NSCLC have a squamous morphology similar to those found in normal lung tissues. The onset of NCC-NSCLC is usually associated with smoking, and the odds of developing the disease are more significant in those who have smoked for long periods or are highly exposed to tobacco smoke than in ordinary people. As a result, SCC-NSCLC usually does not have very well-defined target mutations, and there are relatively few options for targeted therapies. However, in one experiment, doctors randomly assigned 272 patients with advanced squamous cell non-small cell lung cancer to receive therapy with low doses of either nivolumab or doxorubicin. After a year, the trial's findings revealed that patients receiving nivolumab had greater survival and remission rates than those receiving doxorubicin treatment [7].

In the treatment for NSCLC, researchers have used molecules such as PD-1 and CTLA-4 for its immunotherapy, and the results of many experiments have presented a more noticeable effect [8]. Although a single application of either ICIs or chemotherapy can alleviate or cure NSCLC to a certain

extent, the efficiency of monotherapy is not optimistic in comparison and is often accompanied by many side effects, and some patients show resistance to the drugs. Therefore, monotherapy often fails to achieve the desired result in many cases. In recent years, ICIs combined with chemotherapy have attracted widespread attention. When the two are effectively combined, the survival rate of patients can be better enhanced, and this combination therapy has become a vast research trend.

2.3.1 Cooperative interaction

Chemotherapeutic agents frequently employed in clinical practice encompass cytotoxic medications, namely nitrogen mustard, paclitaxel, and platinum pharmaceuticals. These agents typically exert their therapeutic effects by impeding tumor development and proliferation, hence mitigating the deleterious impact imposed by the tumor. Tumor cells employ a strategy to reduce the amount of antigens they release, which involves the inhibition of both antigen presentation and antigen expression. Chemotherapeutic drugs exert an impact on tumor growth by inducing apoptosis. In addition to this effect, they also influence specific subsets of immunosuppressive cells, including regulatory T-cells. Consequently, the normal functioning of these cells may be disrupted, resulting in a reduction in their population and activity [9]. The curative efficacy of ICIs is significantly enhanced by this notable benefit. Within the tumor microenvironment, the existence of regulating T cells partially inhibits the migration of immune cells, including the inhibition of cytotoxic T lymphocytes. A reduction in the amount of regulatory T-cells is correlated with a simultaneous reduction in immunosuppression, hence augmenting the effectiveness of immune checkpoint inhibitors. Chemotherapeutic agents elicit an inflammatory reaction, leading to the secretion of pro-inflammatory cytokines. These chemicals possess the capability to attract immune cells to the local region of the cancer, hence increasing their infiltration and density. T lymphocytes and NK cells possess the ability to engage in direct interactions with target cells, resulting in their elimination [10]. The synthesis of these substances leads to a decrease in the quantity and functionality of immunosuppressive cells, hence augmenting the efficacy of the immune response. Apoptosis may be induced in tumor cells as a result of exposure to chemotherapeutic drugs. During the process of apoptosis in tumor cells, certain chemicals containing antigenic information, such as distinct intracellular proteins, are liberated into the extracellular milieu. These compounds have the capacity for prospective identification by the immune system, thereby initiating an immunological response. The simultaneous administration of chemotherapy and ICIs demonstrates a synergistic effect, augmenting the immune response by activating immune cells that selectively identify tumor antigens. Consequently, this treatment strategy significantly amplifies the therapeutic efficacy of the combined therapy.

The effectiveness of a monoclonal antibody targeting PD-1, when used in combination with chemotherapy, has been evaluated within the framework of the KEYNOTE-021 Phase 2 clinical trial, which was initiated by the pharmaceutical company Merck. The primary objective of this study was to examine a cohort of individuals who had been diagnosed with chemotherapy-primed, Stage III, or IV NSCLC and did not possess a targeted EGFR or ALK mutation. The trial consisted of a cohort of 123 participants, of which 60 were allocated to the treatment group receiving a combination of pembrolizumab, pemetrexed, and cisplatin. The remaining 63 individuals were assigned to the control group, receiving only pemetrexed and cisplatin. The group receiving combination treatment demonstrated significantly greater rates of overall response rate and progression-free survival (PFS) in comparison to the group receiving chemotherapy alone (55% versus 29%, 13.0 months versus 8.9 months) [11].

The principal objective of the phase III clinical trial IMpower131 was to assess the effectiveness of the concurrent administration of chemotherapy and a monoclonal antibody targeting PD-L1, namely atezolizumab, as a potential innovative initial treatment approach for squamous NSCLC. The findings derived from phase III of the IMpower131 trial suggest that the simultaneous administration of atezolizumab in conjunction with Cisplatin and nab-paclitaxel regarding the administration of advanced SCLC did not exhibit a statistically significant enhancement in the median overall survival when compared to the control cohort. The efficacy of pembrolizumab was found to be more

favorable than the comparative effectiveness of combination therapy in the management of epithelial NSCLC. The clinical trial, commonly referred to as KEYNOTE-407, produced findings that demonstrate the efficacy of pembrolizumab when combined with chemotherapy. The findings suggest that the use of this combined therapeutic approach yielded an average overall survival of 15.9 months, signifying a noteworthy prolongation of 4.5 months in comparison to the administration of chemotherapy as a standalone treatment. In contrast, the IMpower131 study showed a notable enhancement in the PFS when atezolizumab was administered with Cisplatin + nab-paclitaxel, as opposed to the utilization of chemotherapy alone. Furthermore, the implementation of combination therapy yielded a significant decrease of 29% in the likelihood of recurrence and metastasis, in comparison to the administration of chemotherapy as a standalone treatment [12]. While the IMpower131 research demonstrated a respectable average PFS, the inability to conceal the absence of achievement in attaining the basic goal of general survival was evident.

In contrast to the positive results found in the KEYNOTE-407 study, which demonstrated good outcomes such as survival without progression and general survival, atezolizumab has faced a temporary obstacle in its prospective utilization as an initial treatment choice for squamous NSCLC. The results of giving atezolizumab together with chemotherapy to those who have high levels of PD-L1 expression, however, show significant promise. As a result, it is predicted that atezolizumab will be approved for use in conjunction with chemotherapy for specific subtypes of cancer that express PD-L1 in the near future.

2.3.2 Suppression of Tumor Blood Supply

VEGF is an important factor used in the body for angiogenesis and regulation. Specifically, VEGF can be classified into subtypes, [1]3and these factors can bind to their receptors, VEGFR-1 and VEGFR-2, resulting in the stimulation of vascular endothelial cells, which detach from their original location and forming new vascular structures [13].

The high rate of metabolism during tumor growth leads to local hypoxia. And due to the body's mechanisms, the hypoxic environment is a potent inducer. Under such conditions, tumor cells are stimulated to produce VEGF and modulate oxygen-sensing factors to make VEGF synthesis more rapid. On the other hand, tumor microenvironment angiogenesis can also be stimulated by factors such as TNF-α, which releases more VEGF and accelerates angiogenesis [14].

Certain chemotherapy medicines can impede the growth of vascular endothelial cells. Anti-angiogenic chemotherapeutic agents can be primarily categorized into two groups: anti-VEGF antibodies and kinase tyrosine inhibitors. Bevacizumab is a frequently utilized pharmaceutical agent within the class of vascular endothelial growth factor (VEGF) antibodies. This antibody binds to VEGF molecules, thus preventing VEGF from binding to its receptor to generate blood vessels [15]. As for tyrosine kinase inhibitors, the main drugs are Sorafenib and Sunitinib, which can inhibit the tyrosine kinase activity of VEGFR, thus blocking its downstream signaling pathway, and then can achieve the purpose of inhibiting the growth of tumor vascular endothelial cells [16]. The inhibition of tumor angiogenesis by chemotherapy can also destroy vascular structures, such as damaging the vessel wall and causing vasoconstriction or intravascular coagulation. These effects indirectly lead to the reduction of blood and nutrient supply inside the tumor [13]. The growth rate of NSCLC is very rapid, which also means that the growth of lung cancer requires more oxygen and nutrients, which shows its dependence on the tumor vasculature. The absence of vascular protection exposes the tumor cells to the immune system when combination therapy using ICIs is more likely to work.

4. Summary

Immunotherapeutic agents combined with chemotherapy have become an essential means of treatment for some NSCLC patients, and the treatment results have shown improved near-term and long-term efficacy. Traditional treatment modalities have certain limitations, especially for advanced NSCLC patients without driver mutations; combining conventional treatment with immunotherapy can provide synergy and complementary advantages, bringing hope to lung cancer patients. Although,

several clinical trials of chemotherapy combined with ICIs are currently underway. However, while improving the efficacy of the combination, it also brings new challenges for researchers and clinical practitioners. Issues such as how to choose the right combination drug, combination dose and appropriate timing of combination, and how to avoid adverse effects of drug combination must be considered deeply. In addition, further confirmation is needed to confirm whether chemotherapy will damage killer immune cells and adversely affect the generation of long-term immune memory cells. It is expected that more high-quality, multicenter, randomized controlled clinical studies will explore the confirmation in the future, which will bring hope to NSCLC patients and even other cancer patients.

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