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Research Progress in the Application of Immune Checkpoint Inhibitors for Renal Cell Carcinoma

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Abstract. In recent years, immune checkpoint inhibitors (ICIs) have made significant progress in the treatment of renal cell carcinoma (RCC). Especially, the PD-1, PD-L1, and CTLA-4 inhibitors have significantly improved the therapeutic efficacy and prognosis of some patients with kidney cancer. This article reviews the research progress and representative drugs of ICIs in the treatment of RCC, such as nivolumab, pembrolizumab, and Ipilimumab, and analyzes their therapeutic advantages and combination treatment strategies. At the same time, this article also points out that there are still challenges such as heterogeneity of therapeutic efficacy, drug resistance, toxic side effects, and difficulties in evaluating therapeutic efficacy (such as pseudoprogression and hyperprogression). To improve treatment effectiveness, future research should focus on precise population screening, biomarker development, combined therapy, and new nanoscale drug development. In conclusion, although ICIs show great potential in the treatment of RCC, their broad application still requires more mechanism exploration and support from individualized treatment strategies.

Keywords: immune checkpoint inhibitors, renal cell carcinoma, monoclonal antibody, kidney cancer

1. Introduction

Renal cell carcinoma (RCC) has become one of the most common and lethal diseases of the urinary system. Its global incidence and mortality have been steadily rising since 1970, posing a threat to public health [1]. Among all RCC subtypes, the clear cell RCC (ccRCC) is the most prevalent, which accounts for 60% to 80% of all cases [2]. These condition highlights the severity of RCC. In order to alleviate the public health burden of RCC, multiple treatment strategies have been developed over the past decades. In conventional treatment methods, the most common one was surgery, including radiotherapy and chemotherapy. However, the effects of these treatment methods were not satisfactory [1]. After that, the target therapies gradually came into people's sight [1]. Particularly, tyrosine kinase inhibitors (TKIs) targeting the vascular endothelial growth factor (VEGF) pathway and the inhibition of the mechanistic target of Rapamycin (mTOR) signaling pathway have been widely used [1]. To be specific, the tumor secretes the VEGF signals, which promotes angiogenesis to supply oxygen and nutrients for tumor growth and facilitate their metastasis [3]. TKI drugs can prevent VEGF receptors from transmitting signals, and this further

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blocks angiogenesis. Thereby depriving the vascular and nutrient support for tumors and hindering disease progression [3]. As for the mTOR pathway, it is responsible for controlling cell growth, metabolism, and proliferation [4]. When mTOR inhibitors disrupt these signals, it is able to suppress tumor cell expansion and survival. Nevertheless, many researchers have demonstrated that TKI drugs are toxic and have side effects, and they have shown resistance in many people [3]. The limitations exhibited by these drugs have compelled researchers to continue exploring more effective and optimal methods for treating RCC.

Until recent years, the appearance of the immune checkpoint inhibitors (ICIs) has changed the treatment landscape for RCC. The ICIs are a kind of medicine that helps the body fight against cancer. The immune system in the human body is sometimes restricted to avoid auto-immune. However, the cancer cells can use this mechanism to evade attacks from immune cells, especially T cells. The function of ICIs is to release the restriction on the immune system and enable immune cells to re-recognize and attack cancer cells [5]. Compared to traditional therapies, ICIs can reactivate the immune system and restore antitumor immunity more efficiently, offering more durable efficacy [3]. In addition, this immunotherapy is particularly effective for metastatic RCC and ccRCC [2, 6]. Despite the ICIs having many clinical benefits, they are not universally effective. Many patients also exhibit primary drug resistance or gradually acquire resistance [7]. Moreover, the therapeutic effect varies between individuals [8]. Therefore, this paper aims to summarize recent progress in ICI-based therapies for RCC, analyze current limitations, and propose recommendations for improvement.

2. The current progress of immune checkpoint inhibitors in treating renal cell carcinoma

2.1. The mechanisms of ICIs

Immune checkpoints are pathways in the immune system and are responsible for regulating the activity of T cells [9]. There are two types of immune checkpoint molecules. The co-stimulatory checkpoint molecules like CD27, CD28, and CD137 can activate the T cells to fight pathogens. While the co-inhibitory checkpoint molecules, such as PD-1 and CTLA-4, inhibit T cells to prevent autoimmune disease and excessive inflammation [9]. However, in the context of the tumor among cancer patients, the co-inhibitory checkpoint molecules will overexpress and interact with ligands. This suppresses the activity of T cells against tumor cells, a phenomenon known as immune evasion [9]. In response to this situation, the mechanism of ICIs is to block the interaction between the checkpoint molecules and ligands [10]. One inhibition of T cells happens when the PD-L1 molecule on tumor cells combines with the PD-1 molecule on T cells. Anti-PD-L1 or anti-PD-1 antibody can be used to block the interaction [5]. The other critical inhibition appears when the B7-2 on an antigen-presenting cell (APC) interacts with the CTLA-4 molecule on T cells. Similarly, anti-CTLA-4 antibody can be used to block this interaction [5].

2.2. Representative drugs and experimental data

Monoclonal antibodies targeting three targets (PD-1, PD-L1, and CTLA-4) have been continuously developed and applied in clinical practices. Objective response rate (ORR) and Overall Survival (OS) are two critical indicators in data. ORR represents the portion of the patients who experience a measurable reduction in tumor size [10]. OS refers to the length of time from treatment initiation until death. This section provides an overview of the clinical data and therapeutic efficacy of several representative drugs. Nivolumab is a PD-1 targeted inhibitor. In a controlled trial, Nivolumab

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showed better efficacy than the mTOR inhibitor Everolimus. The specific result is that among 821 patients with RCC, Nivolumab had a higher median OS of 25.0 months than Everolimus of 19.6 months. Also, an ORR of 25% compared to 5% [10]. Pembrolizumab is another PD-1 inhibitor, showing a good therapeutic effect. It had an ORR of 36.4% in a phase II trial of 110 treatment-naive patients. About 64% had lasting good effects for over one year. Over 70% patients were still alive after two years. [8] Atezolizumab is a PD-L1 inhibitor. It demonstrated an ORR of 15% and a median OS of 28.9 months in a phase I trial among 70 metastatic RCC patients. The number of patients experiencing side effects of grade 4 or below accounted for 15%. Atezolizumab has relatively controllable safety and stable efficacy [1]. Ipilimumab is a CTLA-4 inhibitor. It had a relatively limited efficacy with its ORR of 13% in a phase II trial. Additionally, 33% RCC patients suffered from side effects of grade 3 or 4, such as enteritis and rashes [10].

2.3. Combination medication strategies and their effects

According to the experimental data above, the effect of some ICIs immunotherapies is not perfect. Some research works found that the combination of ICIs and other drugs or the combination of several ICIs can enhance the therapeutic effect. The first one is the combination of PD-1 or PD-L1 inhibitors and CTLA-4 inhibitors. This combination can further activate T cells through multiple processes to enhance the immune system. For instance, the regimen of Nivolumab combined with Ipilimumab achieved a high ORR of 43% in clinical trials [1]. Moreover, this treatment showed remarkable efficacy for medium- and high-risk patients, and some low-risk patients achieved long-term remission [1, 2]. The second category is the combination of PD-1 or PD-L1 and anti-angiogenic drugs like TKIs. These drugs can improve the vascular environment of tumors, enabling T cells to have better infiltration in tumor tissues, thus enhancing the immune efficacy. For example, researchers found that the combination of Pembrolizumab and Axitinib can treat advanced RCC effectively [7]. Thirdly, the immunotherapies can be combined with other treatments like radiotherapy. Radiotherapy can release more tumor antigens and help activate the immune system. In a study, the combination of Pembrolizumab and radiotherapy controlled the RCC in 83% of patients [11].

3. Limitations of ICIs and challenges

3.1. Heterogeneity of therapeutic effect: ineffectiveness for some patients

Although some ICIs achieved significant efficacy in many patients with RCC, there are individual differences in treatment. Some patients showed no response at all after receiving ICI treatment. While the other part is effective initially, they acquire drug resistance or experience severe side effects during the treatment [3]. The reason for this heterogeneity is that individuals with high PD-L1 positive expression are more likely to respond to the treatment. Patients with low PD-L1 expression have poor treatment outcomes, and it would be better for them to be treated with chemotherapy [12]. Therefore, ICI treatment varies from person to person.

3.2. Drug resistance

The drug resistance of ICIs is also one of the difficult problems. There are mainly two forms of drug resistance in ICI immunotherapy. The one is primary resistance, which means the patient shows no response to the drug from the very beginning. The other one is acquired resistance. It refers to the situation where the patient initially responded well, but gradually developed drug resistance and

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became ineffective as the treatment time prolonged [7]. Albert Gang and other researchers further emphasized the universality of this problem. The individual differences in tumor heterogeneity and other factors can lead to drug resistance to different extents [6]. Without a doubt, it is a huge challenge to achieve long-term therapeutic effects.

3.3. Toxicity and side effects

Compared to traditional targeted drugs, ICIs have a stronger ability to activate the immune system and better efficacy [3]. However, the immune-related adverse events (irAEs) are innegligible problems that need to be considered. These side effects include autoimmune diseases and self-attack in multiple organs, causing symptoms like enteritis and rash [10, 13]. In severe cases, the ICI treatment may need to be stopped, or immunosuppressive agents may be used for intervention [13].

3.4. Pseudoprogression (PP) and Hyperprogression (HP): challenges in assessing treatment response

During the treatment of ICIs, the evaluation of therapeutic effects on tumors is also a challenge. PP refers to the temporary enlargement of the tumor in the early stage of treatment. This is actually caused by immune cell infiltration rather than the true deterioration. The tumor will be manifested as increased volume on the image, but then it will experience significant reduction, indicating the treatment is effective [14]. A phase II study showed that 20% of patients with urothelial carcinoma experienced a delayed response after initial treatment. Therefore, the strategy of treatment beyond progression is often adopted in the clinic to avoid erroneous judgment [14]. Correspondingly, HP refers to the accelerated growth of the tumor during the immunotherapy. The growth rate is even twice as before the treatment [14]. This is because the immune system was misled, which stimulates the rapid development of the tumor instead. Champiat et al. pointed out that HP occurs in approximately 9% patients with the tumor. Among them, the proportion of patients with urothelial carcinoma is up to 25% [15]. Hence, this makes a higher demand on the individualized assessment of immunotherapy.

4. Future research directions

In order to overcome the limitations and challenges mentioned above, further research can focus on the following key directions to improve the treatment methods and clinical outcomes. To address the issue of drug resistance, more in-depth research can be conducted on the combination therapy strategies mentioned above. ICI can serve as the main approach, with the anti-vascular drugs, chemotherapy, radiotherapy, or the epigenetic modification drugs as supplements [12]. Further clinical practices and RCC models can be conducted and used to check the effectiveness. The nanoscale drugs have a promising prospect. Studies have shown that nanomaterials can deliver drugs more precisely to the tumor tissues and enhance the activity of macrophages in killing cancer cells. Moreover, the nanoscale drug can simultaneously carry multiple drugs. Specifically, they can deliver drugs such as ICIs and auxiliary drugs to the tumor area, thereby reducing the damage to normal tissues. For instance, ICIs and autophagy inhibitors have achieved better results in the treatment of breast cancer [12]. Hence, the design of the nanoscale drug can be further optimized and verified in the RCC model to enhance its immune effect. It was mentioned earlier that individuals with high PD-L1 expression are more likely to benefit, so PD-L1 can be used as a biomarker. At the same time, other biomarkers like tumor-infiltrating lymphocytes can also be used

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as a biomarker to screen the suitable population [12]. For the patients who can benefit from ICIs, continue to use this method. For the patients who are not very suitable, customize other treatment plans. In the future, through establishing a screening system centered on PD-L1 and other biomarkers, it is expected to achieve more precise immunotherapy strategies for RCC patients. This is also expected to improve efficacy, reduce side effects, and move toward personalized medicine.

5. Conclusion

In recent years, ICIs have made significant breakthroughs in the treatment of RCC. Particularly, drugs targeting the PD-1 or PD-L1 pathway including Nivolumab, Pembrolizumab, and Atezolizumab, and the CTLA-4 pathway including Ipilimumab. These ICIs have demonstrated excellent efficacy in prolonging patient survival and improving tumor response rates in multiple clinical studies. They are responsible for preventing immune evasion and activating T cells, which enables the body to attack the cancer cells more effectively. This provides new hope for many patients, especially for those who are not eligible for surgery. However, immunotherapy still faces many challenges. For instance, not all patients can benefit from it due to the heterogeneity in treatment efficacy. Some individuals may suffer from drug resistance, meaning they cannot respond well to ICIs treatment. Additionally, some patients may experience severe side effects. They are autoimmune inflammatory conditions caused by the immune system attacking normal organs. The treatment evaluation is also complex, with phenomena like PP and HP that can mislead clinical judgements. To overcome these issues, scientists are exploring new methods such as combined therapy, population screening, and developing nanoscale drugs to enhance the efficacy of treatment. In the future, if treatment plans can be individualized for patients' specific conditions, it is expected to further enhance the treatment effect and improve the quality of life of patients. Immunotherapy for kidney cancer is still advancing. It is believed that with further research, there will be more breakthroughs in the future.

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