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PD-1 and PD-L1 Treatment in Renal Cell Carcinoma

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Abstract. Renal cell carcinoma as the top10 diagnosed cases of cancer. The treatment strategies such as surgical or ablative therapies works on early diagnosed patients but rarely works on metastatic RCC patients. However, nearly 30% of patients developed into metastases. As the common strategies that target the VEGF pathway, resistance is common in tumours, thus, more promising method development is imperative. To overcome the evasion strategies, immune checkpoint inhibitors is promising treatment strategies. For renal cell carcinoma treatment, the anti-PD-1 medicine, Nivolumab and Pembrolizumab, and anti-PD-L1 medicine, Avelumab shows better outcome under the clinical trials. Despite the resistance situation occurs in some cases, immunotherapy anti-PD-1 and anti-PD-L1 showed better outcomes in both ORR and OS compare with targeted molecular monotherapy. Recently, the combination of anti-PD-1 or anti-PD-L1 with targeted drug (for example, TKI) or other type of immune checkpoint inhibitor (for example, CTLA-4) provides new perspectives.

Keywords: PD-1, PD-L1, cancer

1. Introduction

Renal cell carcinoma (RCC) was diagnosed in 403,262 cases and involved 175,098 deaths in the world in 2018. The age of diagnosis is concentrated in the 60, and twice as many men are diagnosed as women. In 2020, there were 431,288 diagnosed cases involving 179,368 cases of deaths. Clear cell RCC takes up 70% of all cancers in the kidney. The possible reason leads to Clear cell RCC associated with loss or mutation of the von Hippel-Lindau (VHL) tumour suppressor gene. Although it can be early diagnosed and treated with surgical or ablative therapies, up to a third of cases will develop into metastases. The treatment method for RCC changed greatly with the development. The common treatment methods such as nephrectomy and laparoscopy, ablative therapies, and mandatory node dissection were used for localized disease management. For metastatic disease, the most common strategies were cytoreductive nephrectomy and systemic drugs. However, in the clinical trials of cytokines, high-dose interleukin 2 (IL-2) showed no difference in overall survival. Immune checkpoint blocking agents provide new perspectives for renal cell carcinoma treatment [1].

The immune system takes responses as the body is infected by cancer cells. The cycle of the immune system response against cancer cells is called the Cancer-Immunity cycle. Firstly, dendritic cells (DCs) capture and process the neoantigens released by oncogenesis to active anticancer T cell response. Secondly, neoantigens are captured by DCs and lead to effector T cell response activated against the cancer-specific antigens. Thirdly, the activated effector T cells traffic to the tumour bed and infiltrate the tumour bed. Finally, targeted cancer cells are killed through T cell receptors (TCR) interacting with its cognate

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antigen bound to MHCI and cancer cells recognized and bound by effector T cells. The cycle is iterative to ensure immune response effectively. Thus, more tumour-associated antigens are released, and immune responses become depth. However, in cancer patients, tumour-associated antigens might not be detected due to DCs and T cells recognizing antigens as self-cells [2].

The response of T cell to an epitope is limited by the affinity of both presenting MHC molecule for T cell and MHC-peptide complex for TCR. One problem for cancer immunotherapy is that T cell response elicited by natural tumour antigens weakly might be due to tolerance between high-affinity T cells and antigens. A more potent way is to increase MHC-peptide-TCR complex stability through substitute amino acid of the natural MHCI-restricted tumour antigen, which leads to T cells specific for natural tumour epitope expansion enhanced. Evasion strategies are enabled for both weakly and strongly immunogenic antigens due to the antitumour T cell response being subverted by modulating factors. To overcome the tumour evasion strategies, immune checkpoint blockade is one of the most promising methods in cancer treatment. The overall strategy for cancer immunotherapy is to interrupt the suppressive circuit to enhance the immune response [3].

2. Structure, expression , and signalling pathways

The expression of PD-1 is induced by immune cells, and upregulated PD-1 on tumour-reactive T cells is contributes to T cells exhaustion [7]. The transcription of PD-1 is triggered. The upstream of the PD-1 gene has two conserved regions, CR-B and C0R-C which contain a NFAT binding site. In TCD4 and TCD8 cells, the NFAT binding site is attached to NFATc1 (NFAT2) [7]. NFATc1, c-Fos, and Blimp-1 are transcription factors that enhanced PD-1 expression [8]. The expression of PD-1 can be enhanced by several strategies. During Ag detection, a binding site of CR-B is connected by c-FOS, leads to enhance PD-1 expression after TCR stimulation. In the naive T cells, the promoter region of the pdcd1 gene is bounded by activated NFATc. In the exhausted T cells, it is bounded by interferon α (IFNα), PD-1 promoter is demethylated and expressed in exhausted TCD8 cells, and the expression of PD-1 increases as FOXO1 transcription factor binds to PD-1 promotor in these cells. In addition, the expression of PD-1 is enhanced by increased c-FOS expression due to cancer cell leakage, nuclear factor κB (NF-κB) p65 binds to CR-C, and cytokines (IL-1, IL-21, IL-15, IL-7, and Type1 IFNs). IL-6 and IL-12 enhanced the expression of PD-1 in spleen TCD8 cells [7].

Not only expressed in immune cells and professional APCs, but PD-L1 is also expressed on non-professional APCs that present cytotoxic CD8+ T cells antigen [9]. The expression of PD-L1 is induced

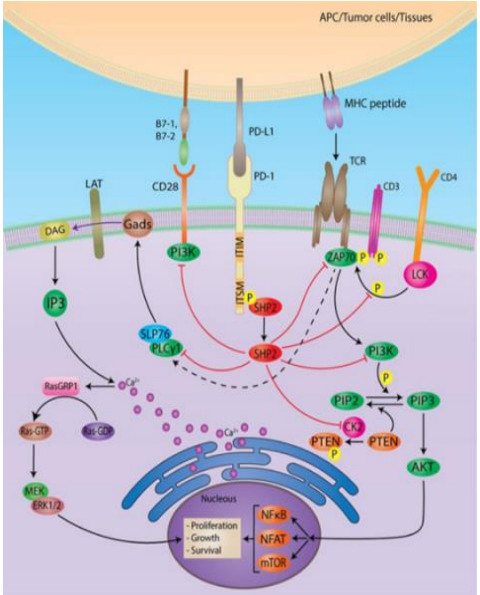

Figure 1. PD-1/PD-L1 signaling pathway [7].

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on the surface of nonhematopoietic, and the presence of PD-L1 is essential for autoimmune damage prevention in peripheral tissues. PD-L1 gene is upregulated by PolyC because of increased reactive oxygen species production and NF-κB activation (figure 1) [7].

3. The mechanisms and development of anti-pd1 and anti-pd-l1

3.1. Nivolumab

Nivolumab was approved by FDA in 2005. The poor prognosis in RCC is associated with the immunosuppressive function of PD-L1. Therefore, nivolumab therapy might restore antitumour immunity by disrupting PD-1 and PD-L1 interaction [10]. In phase II, the PFS, which represents the dose-response relationship, ORR, OS, and safety of nivolumab in mRCC patients, were assessed. The results showed that Nivolumab demonstrated antitumour activity with 20-22% ORR and 18.2-25.5 months of OS, and there is no detected dose-response relationship. In phase III clinical trial, everolimus which is an mTOR inhibitor, was compared with nivolumab in advanced RCC. The median OS in nivolumab was 25 months, whereas that of everolimus was 19.6 months. In addition, the ORR of nivolumab (25%) was higher than that of everolimus (5%). The results demonstrated that advanced RCC patients with previous antiangiogenic treatment had longer survival with nivolumab treatment [10].

3.2. Pembrolizumab

Pembrolizumab is a humanized monoclonal immunoglobulin G4 kappa anti-PD1 antibody, and the binding of pembrolizumab to PD1 is devoid of cytotoxic activity [11]. The common strategies like VEGF show poor outcomes in nccRCC, and the IL-2 and interferon α showed no activity in nccRCC patients. The phase II KEYNOTE-427 study (NCT02853344) evaluated the efficacy and safety in both advanced ccRCC and advanced nccRCC patients. Pembrolizumab monotherapy showed 26.7% ORR and 28.9 months of the median OS in overall nccRCC patients, and in subgroups, for example, tumours with high PD-L1 expression, papillary or unclassified histology, pembrolizumab showed promising activity. These results demonstrated that pembrolizumab monotherapy provides antitumour activity durably in untreated nccRCC patients. In a phase 3 trial about ccRCC patients after nephrectomy, the received pembrolizumab group showed significantly longer disease-free survival than the placebo group [12]. All clinical trials demonstrated that pembrolizumab showed antitumour activity and improved disease-free survival among nephrectomy patients at high risk for recurrence.

3.3. Avelumab

Avelumab was approved by FDA to treat advanced RCC in 2019 [13]. Like other immune checkpoint inhibitors, avelumab block the interaction. In addition, avelumab can bind to Fc-γRIII (CD16) receptor and leads to ADCC because its original Fc-region is retained [14]. The CD16 cause rapid activation and degranulation after antibody-coated target cell recognition, and then the tumour cell is lysed by natural killer cells [14]. Avelumab has become the exclusive therapeutic antibody among immune checkpoint inhibitors because of its capacity of avelumab to enhance immune functions. In a study about the efficacy and safety of avelumab monotherapy as either first-line (1L) or second-line (2L) in mRCC patients, the ORR was 16.1% in the 1L subgroup and 10.0% in 2L subgroups, and the median OS of 2L subgroups was 16.9 months. In addition, the 12-month OS rate of 1L subgroups was 83.7%, and that of 2L subgroups was 65%. The results demonstrated the antitumour activity of avelumab monotherapy in mRCC patients, and the safety of avelumab is acceptable (12.9% and 5.05% of 3/4 treatment-related AEs in the 1L and 2L subgroups, respectively).

4. Advantages and disadvantages of anti-pd1 and anti-pd-l1 in rcc treatment

In past decades, anti-PD-1 and anti-PD-L1 therapy achieved excellent success. Immunotherapy anti-PD-1 and anti-PD-L1 blocks the immune checkpoint PD-1 and PD-L1, which has pro-tumour activity [15]. In the study of the safety, activity, and immune correlation of anti-PD-1 therapy investigation among patients with RCC, the rates for all doses were 27%. There were 21% of patients died due to

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disease progression mostly. However, most patients did not show clinical responses, so they cannot benefit from anti-PD-1/PD-L1 therapy. Despite patients responding to anti-PD-1/PD-L1 therapy, acquired resistance developed in a large number of responders after initial responses [15].

5. Improvements

5.1. Combine with anti-CTLA-4

Ipilimumab, a CTLA-4 inhibitor, is approved for advanced RCC treatment after antiangiogenetic therapy. However, the toxic effects of ipilimumab limit its development as a monotherapy. The combination of nivolumab plus ipilimumab showed a higher response rate than either agent alone, and it showed antitumour activity in RCC patients, both pre-treated patients and untreated previously patients. The RCC patient survival rate treated with nivolumab plus ipilimumab was 75% in 18 months, and the ORR was 42% higher than sunitinib's ORR (27%). These results demonstrated that the combination of immune checkpoint inhibitors has promising efficacy and overall survival in advanced RCC treatment [16].

5.2. Combine with TKI

The first-line treatment method for mRCC evolution rapidly. The VEGFR-TKI showed better PFS, OS and response rate compared with sunitinib which is an inhibitor that targets VEGFRs. TKIs have anti-angiogenic effects, which work on the tumour microenvironment and lead to cytotoxic T-cell activation and T-cell infiltration increase to enhance immune checkpoint inhibitors. Pembrolizumab plus axitinib might provide a better outcome of OS, and avelumab plus axitinib might provide a better outcome of PFS. The efficacy-tolerability of the combination, nivolumab plus ipilimumab, is most favourable. However, there is no head-to-head comparison of trials of these novel strategies and no biomarkers. The network meta-analysis showed that immune checkpoint inhibitors combined with TKI provided better OS and PFS. In treatment ranking, nivolumab plus cabozantinib and pembrolizumab plus lenvatinib had the highest possibility of showing better OS and PFS. The combination of immune checkpoint inhibitors with TKIs can enhance tumour expression and improve survival outcomes and is a promising treatment strategy in mRCC treatment.

Clinicians are looking for treatments to help more patients manage their diseases without compromising their quality of life. The new data from CheckMate-9ER are important for patients with first-line advanced renal cell carcinoma as these new data provide evidence of the efficacy benefits of this combination and the good quality of life outcomes reported by patients. RCC with Cabometyx and Opdivo's "targeted + immune" combination regimen showed clinically significant improvement in key efficacy PFS and OS. In addition, Cabometyx combined with Opdivo has good safety.

6. Conclusion

The discovery of a more effective treatment method is crucial for all cancers. Immunotherapy provides insights into cancer treatment. 30% of RCC patients developed metastatic cancer. For metastatic and advanced RCC, surgical or ablative therapies cannot provide better outcomes. The clinical trials about anti-PD-1 and anti-PD-L1 in RCC patients showed positive outcomes. The anti-PD-1 medicine, Nivolumab, showed antitumour activity with 20-22% ORR and 18.2-25.5 months of OS under clinical trials. The clinical trials of Pembrolizumab monotherapy demonstrated the antitumour activity of pembrolizumab in both ccRCC patients and nccRCC patients (26.7% ORR and 28.9 months of the median OS). The anti-PD-L1 medicine, Avelumab, can enhance innate and adaptive immune functions. For the first-line treatment with avelumab among mRCC patients, the outcome showed 16.1% ORR and 83.7% 12-month OS rate of 1L subgroups. All these treatment strategies showed antitumour activity and safety under clinical trials. However, resistance is also present in anti-PD-1 and anti-PD-L1 treatment. The combination of nivolumab plus ipilimumab showed a 75% 18 months overall survival rate and 42% ORR. Despite the excellent outcomes of the combination treatment strategies, resistance still needs to be considered.

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References

[1] E. Jonasch et al, Renal cell carcinoma. BMJ 349, g4797–g4797 (2014).
[2] D. S. Chen et al, Oncology Meets Immunology: The Cancer-Immunity Cycle. Immunity 39, 1–10 (2013).
[3] A. Sukari et al, Cancer Immunology and Immunotherapy. Anticancer Res. 36, 5593–5606 (2016).
[4] N. Patsoukis et al, Revisiting the PD-1 pathway. Sci. Adv. 6, eabd2712 (2020).
[5] D. M. Pardoll, The blockade of immune checkpoints in cancer immunotherapy. Nat. Rev. Cancer 12, 252–264 (2012).
[6] Y. Xu et al, Current status of antigen-specific T-cell immunotherapy for advanced renal-cell carcinoma. Hum. Vaccines Immunother. 17, 1882–1896 (2021).
[7] A. Salmaninejad et al, PD-1/PD-L1 pathway: Basic biology and role in cancer immunotherapy. J. Cell. Physiol. 234, 16824–16837 (2019).
[8] C. Li et al, ADAP and SKAP 55 deficiency suppresses PD -1 expression in CD 8 + cytotoxic T lymphocytes for enhanced anti-tumor immunotherapy. EMBO Mol. Med. 7, 754–769 (2015).
[9] L. M. Francisco et al, The PD-1 pathway in tolerance and autoimmunity: PD-1 pathway, Tregs, and autoimmune diseases. Immunol. Rev. 236, 219–242 (2010).
[10] R. J. Motzer et al, Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma. N. Engl. J. Med. 373, 1803–1813 (2015).
[11] G. Kwok et al, Pembrolizumab (Keytruda). Hum. Vaccines Immunother. 12, 2777–2789 (2016).
[12] T. K. Choueiri et al, Adjuvant Pembrolizumab after Nephrectomy in Renal-Cell Carcinoma. N. Engl. J. Med. 385, 683–694 (2021).
[13] B. Zhao et al, Efficacy and safety profile of avelumab monotherapy. Crit. Rev. Oncol. Hematol. 166, 103464 (2021).
[14] G. Hamilton et al, Avelumab: combining immune checkpoint inhibition and antibody-dependent cytotoxicity. Expert Opin. Biol. Ther. 17, 515–523 (2017).
[15] Q. Lei et al, Resistance Mechanisms of Anti-PD1/PDL1 Therapy in Solid Tumors. Front. Cell Dev. Biol. 8, 672 (2020).
[16] R. J. Motzer et al, Nivolumab plus Ipilimumab versus Sunitinib in Advanced Renal-Cell Carcinoma. N. Engl. J. Med. 378, 1277–1290 (2018).