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Perspective

HIF1A predicts the efficacy of anti-PD-1 therapy in advanced clear cell renal cell carcinoma

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ABSTRACT

Immunotherapy for cancer has become a revolutionary treatment, with the progress of immunological research on cancer. Cancer patients have also become more diversified in drug selection. Individualized medical care of patients is more important in the era of precision medicine. For advanced clear cell renal cell carcinoma (ccRCC) patients, immunotherapy and targeted therapy are the two most important treatments. The development of biomarkers for predicting the efficacy of immunotherapy or targeted therapy is indispensable for individualized medicine. There is no clear biomarker that can accurately predict the efficacy of immunotherapy for advanced ccRCC patients. Our study found that HIF1A could be used as a biomarker for predicting the anti-PD-1 therapy efficacy of patients with advanced ccRCC, and its prediction accuracy was even stronger than that of PD-1/PD-L1. HIF1A is expected to help patients with advanced ccRCC choose therapeutic drugs.

Introduction

As scientists make great progress in the biology of cancer, the choice of treatment for cancer patients shows a variety of situations. The drug treatment of renal cell carcinoma has changed from the initial non-specific immunotherapy (IFN-α and IL-2) to targeted therapy, specific immunotherapy (PD-1/PD-L1, CTLA4), and combined immunotherapy with targeted therapy [1,2]. However, the diversity of drug development is not the original intention of precision medicine, and it cannot achieve the purpose of individualized medicine. It is the most important requirement to choose the most suitable drug for different patients. The development of biomarkers that can predict the efficacy of immunotherapy and targeted therapy is an urgent problem to be solved. For patients with advanced ccRCC, there are no biomarkers that can accurately predict the effectiveness of immunotherapy. Even PD-1/PD-L1, as the targets of immunotherapy, are limited in predicting the efficacy of immunotherapy [3]. Recent studies have found that PBRM1 and heterozygosity of HLA-1 genes can be used as biomarkers for predicting immunotherapy, but their roles still need large-scale data for clinical verification [4,5]. Therefore, it is of great significance to explore the predictive markers of the immunotherapy response that can be used in clinical practice.

Materials and methods

In this study, the inclusion criteria of patients were advanced (metastatic) renal cell carcinoma of clear cell histology and the disease progressed in at least one systemic antiangiogenic therapy, and treated with nivolumab in CheckMate-025 [6]. We extracted RNA sequencing data and survival data of these patients for analysis. The basic clinical characteristics of the patients can be found in the supplementary material. Patients were divided into high expression group and low expression group according to the median of gene expression. Kaplan–Meier curve analysis was carried out by using log-rank test to compare OS (overall survival) and PFS (progression-free survival). The analysis and visualization of the data in this study were implemented in MedCalc (Version 20.113).

Results

In the CheckMate 025 cohort, we found that the expression of PD-1 at the transcriptomic level was not statistically significant with OS and PFS

Abbreviations: ccRCC, clear cell renal cell carcinoma; OS, overall survival; PFS, progression-free survival.

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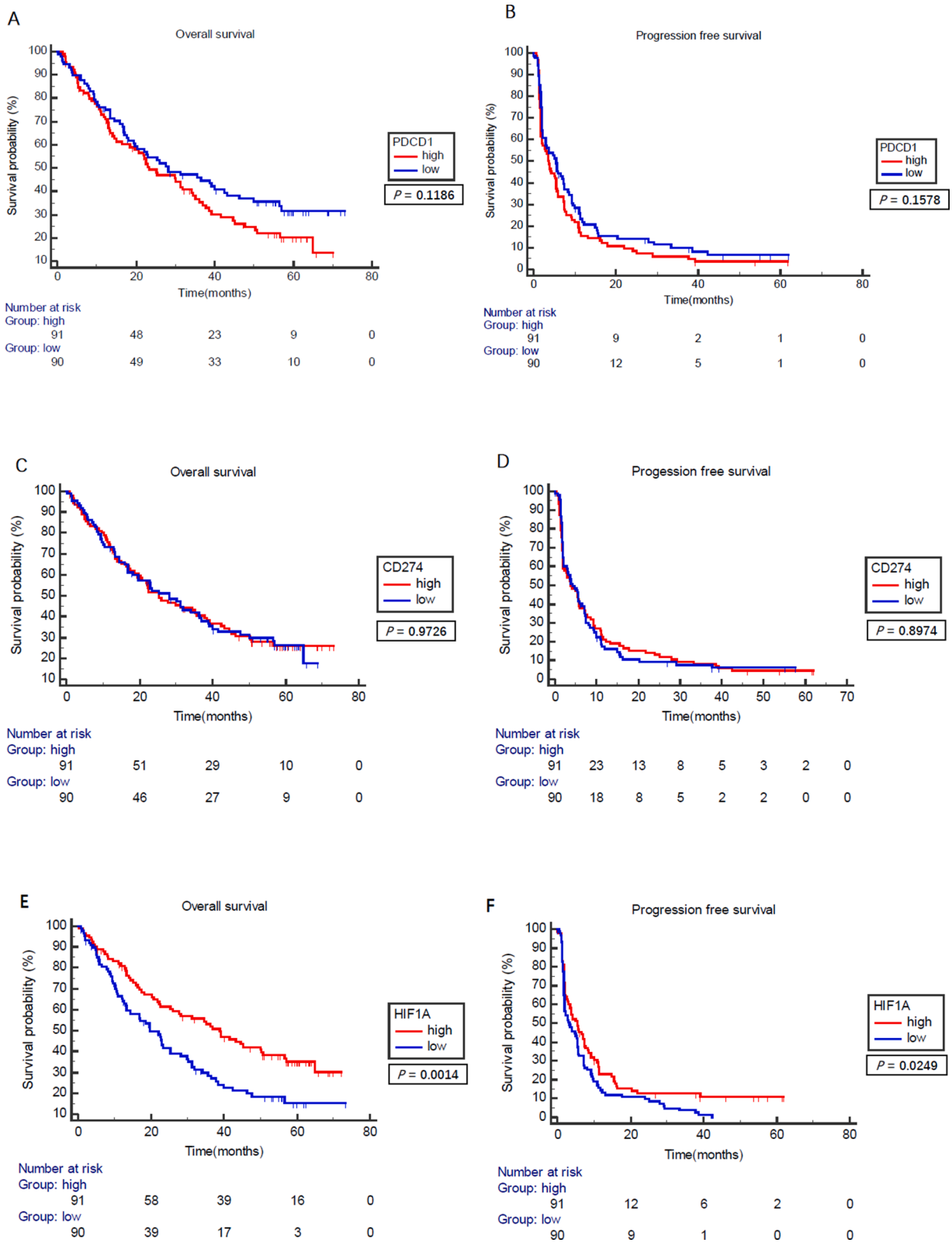

Fig. 1. Kaplan–Meier curves analysis to compare OS and PFS. (A) Comparison of OS probability between PDCD1 high and low expression groups. (B) Comparison of PFS probability between PDCD1 high and low expression groups. (C) Comparison of OS probability between CD274 high and low expression groups. (D) Comparison of PFS probability between CD274 high and low expression groups. (E) Comparison of OS probability between HIF1A high and low expression groups. (F) Comparison of PFS probability between HIF1A high and low expression groups.

in patients with advanced ccRCC, and even had an opposite trend (Fig. 1. A-B). In addition, we also compared whether the expression level of PD-1 ligand PD-L1 was related to the survival of anti-PD-1 therapy in patients with advanced ccRCC, and we obtained similar results that PD-L1 could not predict the effectiveness of anti-PD-1 therapy at the transcriptome level (Fig. 1. C-D). As an upstream molecule of PD-1, HIF1A can promote the expression of PD-1[7]. We believe that HIF1A may serve as a marker for predicting the response of anti-PD-1 therapy. Therefore, we compared the differences in the anti-PD-1 therapy efficacy of patients with different expression levels of HIF1A. Surprisingly, HIF1A can stratify patients well, and the OS of patients with high HIF1A expression was significantly longer than that of the low expression group ($p = 0.0014$), and the PFS of patients with high HIF1A expression was also significantly longer than that of the low expression group ($p = 0.0249$) (Fig. 1. E-F).

Discussion

The main anti-PD-1 drugs currently used in the clinic were nivolumab and pembrolizumab. However, more and more studies have found that the expression level of PD-1 cannot determine the effectiveness of anti-PD-1 therapy [3,8,9]. In this study, we unexpectedly found that HIF1A can be used as a biomarker for predicting the efficacy of anti-PD-1 therapy in patients with advanced ccRCC. Patients with high HIF1A expression showed long OS and PFS after anti-PD-1 therapy.

With the diversification of the treatment of advanced ccRCC patients, the choice of patients was becoming more and more complicated, which undoubtedly highlighted the difficult problem of how to choose different drugs for different patients. In addition to evaluating treatment methods with clinical information, molecular prediction biomarkers were also extremely important. Many clinical trials of immunotherapy and targeted-immune combination therapy have been carried out in the treatment of advanced ccRCC, and they have also become the treatment modalities for advanced ccRCC patients that need to be carefully considered. Therefore, the identification and validation of biomarkers are crucial for optimizing first-line drug selection and treatment sequences.

Currently, there are no predictive biomarkers validated in ccRCC. The use of PD-1/PD-L1 expression levels to predict the efficacy of immunotherapy was untenable in many studies [3]. Recent studies have found that inhibition of HIF1A expression could promote the efficacy of immune checkpoint blockade in many types of cancer [10,11]. However, the role of HIF1A expression in the efficiency of immune checkpoint blockade in advanced ccRCC remained unclear. In this study, we found that the expression of HIF1A could robustly predict the efficacy of anti-PD-1 therapy in advanced ccRCC. Patients with high HIF1A levels were more likely to have longer OS and PFS, which was undoubtedly a major finding. However, large-scale data was still needed for validation before it could be put into clinical use, and even so, this provided a glimmer of hope for doctors and advanced ccRCC patients. Whether HIF1A could be used as a biomarker to predict the response of anti-PD-1 therapy at the protein level remains to be further studied. In addition, the potential mechanism of HIF1A predicting anti-PD-1 therapy response was also worthy of further study.

Conclusion

In conclusion, after anti-PD-1 therapy in patients with advanced ccRCC, we found that the OS and PFS of patients with high HIF1A expression were significantly longer than those of patients with low expression group. Collectively, these results demonstrated that HIF1A can be used as a marker to predict the therapeutic response of nivolumab in patients with advanced ccRCC.

Authors' contributions

Xiang Wang and Siteng Chen performed the study concept and design; Tuanjie Guo performed the development of methodology, writing, review, and revision of the paper; Tao Wang and Jian Zhang provided acquisition, analysis, interpretation of data, and statistical analysis.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Data availability

In this study, the data are derived from supplementary materials in clinical trials CheckMate 025(https://www.nature.com/articles/s41591–020–0839-y). The data used and analyzed in this study are also available from the corresponding author upon reasonable request.

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Declaration of Competing Interest

The authors declare no conflict of interest.

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None.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.tranon.2022.101554.

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