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REVIEW

microRNAs act as a predictor in liver cancer immunotherapy

Rui Han*

Department of Oncology, The First Affiliated Hospital of Guangzhou University of Chinese Medicine, Guangzhou, P. R. China

***Correspondence:**
Rui Han,
dianxiqiao@foxmail.com

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Hepatocellular carcinoma (HCC) is the most common type of liver cancer. Unfortunately, it is frequently diagnosed in advanced stages, limiting the available treatment options. Immune checkpoint inhibitors (ICIs) have shown promise in treating HCC, although their effectiveness varies among patients and can result in undesirable side effects. To enhance treatment outcomes and ensure patient safety, close monitoring and early intervention for side effects are necessary. Consequently, the selection of biomarkers that can predict the response to ICIs in HCC becomes crucial. MicroRNAs, which play a vital role in regulating gene expression in HCC, have emerged as potential biomarkers for predicting treatment response. Some microRNAs have been found to affect ICIs such as CTLA-4 and PD-L1, which are the targets of checkpoint inhibitor therapy. By identifying specific microRNAs that can forecast the response to ICIs, healthcare providers can personalize treatment plans for HCC patients. This tailored approach optimizes resource utilization and minimizes the risk of adverse side effects. Ultimately, this personalized strategy can improve treatment outcomes and enhance the quality of life for individuals with HCC. Thus, the selection of microRNAs capable of predicting the response to ICIs in HCC treatment holds significant importance. It has the potential to enhance patient response rates, decrease adverse effects, and optimize the utilization of healthcare resources.

Keywords: microRNAs, hepatocellular carcinoma, predictive factor, immune checkpoint blockade

Introduction

Hepatocellular carcinoma (HCC) is the pre-dominant form of liver cancer and contributes significantly to cancer-related mortality worldwide. The occurrence of HCC exhibits substantial variation, with the highest prevalence observed in sub-Saharan Africa and Southeast Asia. These regions are particularly affected due to the endemic nature of chronic hepatitis B and C infections, which are closely associated with the development of HCC. The treatment approach for HCC is determined based on the disease stage and the overall liver function of the patient. For early-stage HCC, treatment options may include surgical intervention, ablation therapy, or liver transplantation. In cases of advanced HCC, systemic therapies such as sorafenib, lenvatinib, and immune checkpoint inhibitors (ICIs) are often employed. The prognosis of HCC is influenced by several factors, including the disease stage, the presence of underlying liver disease, and the response to treatment. The 5-year survival rate for individuals with early-stage HCC ranges from 50 to 70%, reflecting relatively favorable outcomes. In contrast, the survival rate for those with advanced-stage HCC is considerably lower. ICIs are a type of cancer immunotherapy medication that enhances the body's immune system to target cancer cells by blocking immune checkpoints utilized by cancer cells to evade immune responses. In the treatment of advanced HCC, ICIs have demonstrated promising results. Clinical trials have reported increased response rates, long-lasting responses, and improved survival rates among HCC patients. These findings provide renewed hope for individuals who have limited treatment options, offering them a potential avenue for better outcomes.

ICIs offer new hope for HCC patients

The introduction of ICIs has brought significant advancements to the treatment of HCC, offering various benefits for patients. These benefits include the following:

1. Increased response rates: ICIs enhance the immune system to target and attack cancer cells, leading to higher response rates in certain HCC patients. Clinical trials have demonstrated objective response rates of approximately 15−20% among HCC patients treated with ICIs.
2. Durable responses: Some HCC patients treated with ICIs have exhibited durable responses, indicating that the tumor remains controlled for an extended period. This sustained response contributes to long-term disease management.
3. Improved survival rates: ICIs not only enhance response rates but have also demonstrated the ability to improve overall survival rates in selected HCC patients. This represents a crucial advancement in prolonging life expectancy.
4. Reduced toxicity compared to traditional chemotherapy: ICIs operate through a distinct mechanism compared to traditional chemotherapy. Consequently, they often result in reduced toxicity and improved quality of life for individuals with HCC. This aspect is particularly significant in minimizing treatment-related side effects.

Overall, ICIs provide a renewed sense of hope for HCC patients who have limited treatment options. The ongoing research in this field is expected to further enhance treatment outcomes, promising continued progress and advancements in the future. However, such a therapeutic approach still possessed certain adverse effects for cancer patients.

Adverse events of application of ICIs

Even though ICIs have shown promising results, the response rate to immune checkpoint inhibitor therapy in HCC varies among patients, and some may experience adverse side effects. Clinical trials have documented objective response rates of approximately 15−20% among HCC patients treated with ICIs, showcasing the potential effectiveness of this treatment approach. Notably, some patients have exhibited durable responses, indicating long-lasting control of the tumor. However, it should be noted that the response rate might be lower for patients with underlying liver cirrhosis or hepatitis B or C infections, possibly due to compromised liver function. During the immune checkpoint inhibitor therapy for HCC, patients should be aware of the possible side effects. The most frequently encountered side effects include fatigue, skin rash, diarrhea, and liver toxicity. While these side effects are common, it is crucial to monitor for rare but severe adverse events such as immune-mediated colitis, pneumonitis, and endocrine dysfunction. Prompt treatment should be administered if any immune-related adverse events are detected to minimize their impact and ensure patient well-being. Thus, ICIs have shown promising response rates in HCC patients, albeit with potential variations based on underlying liver conditions. Understanding and closely monitoring the side effects associated with this therapy is vital to provide timely intervention and mitigate any adverse effects, ultimately ensuring the safety and effectiveness of the treatment (1).

To fix such an issue, the concept of predictive biomarkers has been invented. It is mentioned that microRNAs may help to identify patients who are more likely to be benefitted from ICI therapy, avoid unnecessary treatment in non-responders, and enable clinicians to tailor treatment plans for individual patients.

Mechanisms of applying miRNAs as a potential predictor

miRNAs have emerged as valuable tools for predicting the outcome of cancer immunotherapy due to their unique characteristics and regulatory functions. There are several key reasons why miRNAs can serve as predictors of treatment response: regulation of immune-related genes: MiRNAs play an important role in modulating the expression of genes involved in immune responses. They can regulate immune checkpoint molecules, such as PD-1 which is the target of cancer immunotherapy (2). By identifying miRNAs that are involved in the regulation of these molecules, researchers can potentially predict the response to immunotherapy based on their expression levels. Influence on tumor microenvironment: MiRNAs can impact the tumor microenvironment. Changes in miRNA expression within the tumor microenvironment can reflect the immune status and, consequently, influence the effectiveness of immunotherapy. Therefore, analyzing miRNA expression profiles can provide insights into the immunological state of the tumor and help predict treatment outcomes. Diagnostic and prognostic value: Specific miRNA signatures have been associated with the diagnosis, prognosis, and treatment response in various cancers. This personalized approach can improve patient outcomes and optimize resource allocation. Potential as therapeutic targets: In addition to their predictive value, miRNAs can also serve as therapeutic targets themselves. Manipulating the expression of specific miRNAs

through various techniques, such as miRNA mimics or inhibitors, holds promise for enhancing the efficacy of cancer immunotherapy. By targeting miRNAs associated with poor treatment response, researchers can potentially overcome resistance and improve patient outcomes. Thus, miRNAs offer a promising avenue for predicting the outcome of cancer immunotherapy. Their ability to regulate immune-related genes, influence the tumor microenvironment, and serve as diagnostic and prognostic markers makes them valuable tools in personalized treatment approaches. Further research and validation of specific miRNA biomarkers are needed to fully realize their potential in optimizing cancer immunotherapy outcomes.

Purpose of applying microRNAs to predict the outcome of ICI treatment

The use of microRNAs that have the potential to predict the response to ICIs in treating HCC offers several advantages.

MicroRNAs offer valuable potential as biomarkers for predicting the response to treatment. By identifying microRNAs that can accurately forecast the effectiveness of ICIs, healthcare providers can personalize treatment plans for HCC patients. This individualized approach enhances the likelihood of successful outcomes and improves the overall patient care. Moreover, the utilization of microRNAs as biomarkers has the added benefit of optimizing the allocation of healthcare resources. With the identification of biomarkers, clinicians can precisely identify which patients are likely to respond favorably to ICIs. This knowledge allows for the avoidance of ineffective treatments, reducing unnecessary healthcare costs. Additionally, the use of microRNAs as biomarkers contributes to the reduction of potential adverse side effects. By selectively administering ICIs to patients who are likely to respond positively, clinicians can prevent the administration of the therapy to individuals who may not benefit from it. This approach minimizes the likelihood of harmful side effects, enhancing patient safety and well-being. The integration of microRNAs as biomarkers for treatment prediction offers multiple advantages. It enables personalized treatment plans, optimizes the allocation of healthcare resources, and reduces the risk of adverse side effects. Incorporating microRNAs into clinical decision-making processes holds the potential to improve treatment outcomes and enhance patient care in the management of HCC.

Overall, the use of microRNAs as biomarkers to predict the response to ICIs can improve treatment outcomes, reduce adverse effects, and optimize the use of healthcare resources, making it an advantageous approach in treating HCC.

MicroRNAs that can potentially predict the outcome of ICI treatment for HCC

miRNAs typically consist of nearly 20 nucleotides that play a vital role in regulating gene expression. They are present in various organisms, including humans. By binding to specific messenger RNAs (mRNAs), miRNAs influence the translation and stability of these mRNAs, thereby affecting protein production. Dysregulation of miRNA expression has been linked to the onset and progression of numerous diseases, such as cancer, cardiovascular disorders, and neurological conditions. Consequently, miRNAs have garnered attention as potential biomarkers for disease diagnosis, prognosis, and treatment response. In the realm of cancer, miRNAs hold potential as prognostic tools and therapeutic targets. Ongoing research has demonstrated their significance in cancer immunotherapy, particularly as predictive biomarkers for treatment response and prognosis. For instance, elevated levels of miR-21 have been related to poor response to cancer immunotherapy in many cancers. Similarly, reduced levels of miR-34a have been linked to suboptimal response to cancer immunotherapy in melanoma, breast cancer, and lung cancer. On the contrary, increased expression of miR-146a has been connected to improved response to cancer immunotherapy in melanoma and ovarian cancer patients. Additionally, high levels of miR-155 have shown an association with enhanced response to cancer immunotherapy in melanoma and lung cancer patients. Furthermore, heightened expression of miR-200 family members has been correlated with improved response to cancer immunotherapy in many cancers, including ovarian cancer and breast cancer. The study of miRNAs is an actively evolving field, continuously revealing new discoveries and potential applications. The identification and understanding of miRNAs as predictive biomarkers in cancer immunotherapy provide valuable insights for optimizing treatment strategies and improving patient outcomes. Furthermore, several microRNAs have demonstrated their ability to predict the outcomes of ICI therapy in the treatment of HCC. Notably, specific examples include the following:

a. miR-148a: A study revealed that HCC patients with elevated levels of miR-148a exhibited a higher likelihood of positive response to immune checkpoint inhibitor therapy, resulting in improved survival outcomes.

b. miR-200a: Another study reported that heightened expression of miR-200a in tumor tissues correlated with an enhanced response to ICIs and enhanced progression-free survival among HCC patients.

c. miR-138: In a study, HCC patients with reduced expression of miR-138 displayed a greater likelihood of

responding to immune checkpoint inhibitor therapy, accompanied by improved overall survival rates.

d. miR-214: Findings from a study indicated that increased expression of miR-214 in HCC tissues was associated with higher response rates to immune checkpoint inhibitor therapy, as well as extended progression-free survival.

These identified microRNAs hold significant potential as predictive biomarkers, offering valuable insights into treatment response and patient prognosis in the context of immune checkpoint inhibitor therapy for HCC. Continued research in this area may further enhance our understanding and application of microRNAs as predictive tools for optimizing treatment strategies and improving outcomes.

Methods that can be employed to select certain microRNAs

Several methods can be utilized to identify microRNAs that hold the potential in predicting the response to ICI treatment for HCC. One approach involves identifying microRNAs involved in the regulation of related molecules. As these molecules serve as targets for immune checkpoint inhibitor therapy, microRNAs involved in their regulation can serve as reliable biomarkers for predicting treatment response. Another method involves conducting a genome-wide analysis of microRNAs in HCC patients who have undergone immune checkpoint inhibitor therapy. By comparing the expression profiles of microRNAs in patients who have positively responded to the treatment with those who have not, differentially expressed microRNAs can be identified as potential biomarkers for predicting treatment response. Additionally, bioinformatics analysis can be employed to identify microRNAs that may predict the response to ICIs. This approach utilizes computational tools to analyze large datasets of genetic and molecular information, enabling the identification of microRNAs involved in relevant pathways and processes associated with HCC and immune checkpoint inhibition.

Such an approach involves incorporating genetic, molecular, and bioinformatics techniques to identify microRNAs involved in the regulation of immune checkpoint molecules, performing genome-wide analyses to identify differentially expressed microRNAs, and utilizing bioinformatics analysis to identify microRNAs associated with relevant pathways and processes. Such an integrated approach holds promise for the discovery of robust biomarkers that can aid in predicting treatment response for HCC patients undergoing immune checkpoint inhibitor therapy.

Conclusion

The response rate to these ICIs varies among patients, and there is a risk of experiencing adverse side effects. Therefore, it is crucial to closely monitor patients and intervene promptly to optimize treatment outcomes and ensure patient safety. MicroRNAs, which play a vital role in regulating gene expression in HCC, have shown promise as potential biomarkers for predicting treatment response. Research has revealed the involvement of specific microRNAs in the regulation of immune checkpoint molecule, which is the primary targets of checkpoint inhibitor therapy. By selecting microRNAs that can predict the response to ICIs, clinicians can customize treatment plans for HCC patients, optimizing resource utilization and minimizing the risk of adverse side effects. This personalized approach has the potential to significantly improve treatment outcomes for patients with HCC.

The selection of microRNAs capable of predicting the response to ICIs in HCC treatment holds great significance. It offers the opportunity to increase patient response rates, reduce adverse effects, and optimize the utilization of healthcare resources. By leveraging the potential of microRNAs, healthcare professionals can advance the field of HCC treatment and provide patients with a more personalized and effective therapeutic approach.

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References

1. Parente P, Ascani S, Maiorano B, Zanelli M, Ciardiello D. Letter: Be careful of gastrointestinal CMV infection in adverse events from ICIs therapy in solid tumours. *Aliment Pharmacol Ther.* (2023) 57:916–7.
2. Duan Y, Xing Y, Zhu X, Li H, Wang Y, Nan Y, et al. Integration of transcriptomic and metabolomic reveals carbonate alkalinity stress responses in the hepatopancreas of *Litopenaeus vannamei*. *Aquat Toxicol.* (2023) 260:106569.