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Editorial

Selecting ideal combined immunotherapy for treating HCC

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Abstract

Hepatocellular carcinoma (HCC) is a type of liver cancer that is often diagnosed at an advanced stage, making treatment challenging. Immunotherapy, specifically immune checkpoint inhibitors, has shown promising results in the treatment of HCC. However, not all patients respond to this therapy, and even those who do respond may eventually develop resistance. Therefore, discovering an effective therapeutic approach that can improve the efficiency of immune checkpoint inhibitors in treating HCC is of significant importance. Immune checkpoint inhibitors block these checkpoints, allowing the immune system to recognize and attack cancer cells. However, this approach is not always effective, and there is a need to improve the response rate and durability of response. Discovering an effective therapeutic approach could potentially lead to better treatment outcomes for patients with HCC. It could enhance the efficacy of immune checkpoint inhibitors, increase response rates, and possibly extend the duration of response. Moreover, it may also help overcome resistance to therapy. Selecting effective therapeutic approaches that can improve the efficiency of immune checkpoint inhibitors in treating HCC is critical to improve patient outcomes and ultimately save lives.

Keywords: Combined immunotherapy, Sensitizer, Immune checkpoint inhibitor, Therapeutic strategy

Editorial

The discovery of proper sensitizers for immune checkpoint inhibitors (ICIs) in hepatocellular carcinoma (HCC) treatment represents a significant breakthrough in the field of cancer therapy, but it is still in initial stage [1,2].

HCC is one of the leading causes of cancer-related deaths worldwide [3]. It is often diagnosed at an advanced stage, making it difficult to treat. Traditional treatments for HCC, such as surgery and chemotherapy, have limited effectiveness, and the prognosis for patients with advanced disease is poor [3]. However, the discovery of ICIs has opened up new possibilities for treating HCC. For details, in recent years, the use of immune checkpoint inhibitors (ICIs) has revolutionized the treatment of various types of cancer, including HCC. ICIs, such as programmed cell death protein 1 (PD-1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) inhibitors, have shown remarkable efficacy in advanced HCC, where traditional treatments have had limited success. Immune checkpoint inhibitor monotherapy involves the use of a single agent to block the interaction between immune checkpoint molecules and their ligands, releasing the brakes on the immune system and enabling it to attack cancer cells. In HCC, PD-1 inhibitors such as nivolumab and pembrolizumab have been approved by the US Food and Drug Administration (FDA) for the treatment of advanced HCC. These drugs have shown promising results, with objective response rates of up to 20% and improved overall survival compared to standard of care. However, immune checkpoint inhibitor monotherapy has its limitations, such as low response rates and the development of resistance over time [4]. In addition, some patients may experience adverse effects, including immune-related toxicities. Therefore, combination therapies with proper sensitizers hold great promise for improving the overall response rates and prolonging the survival of patients with HCC [4].

Immune checkpoint inhibitors based therapy involves the use of ICIs in combination with other therapies, such as chemotherapy, radiation therapy, or targeted therapy. The combination of

nivolumab and ipilimumab (a CTLA-4 inhibitor) has been shown to improve response rates and prolong survival in advanced HCC patients, compared to nivolumab alone. In addition, the combination of nivolumab and ipilimumab with chemotherapy agents such as doxorubicin or gemcitabine has demonstrated promising results in clinical trials. Targeted therapies, such as sorafenib and lenvatinib, have also been used in combination with ICIs in HCC treatment. The combination of lenvatinib and pembrolizumab has shown improved response rates and longer progression-free survival compared to lenvatinib alone in patients with advanced HCC [5]. Thus, combination therapies with proper sensitizers hold great promise for improving the overall response rates and survival outcomes for patients with HCC. Further studies are needed to optimize the selection of sensitizers and improve the efficacy of combination therapies [5].

Existing sensitizers for ICIs in HCC are, for instance, chemotherapy agents such as doxorubicin and 5-fluorouracil [6,7], targeted therapies such as sorafenib and Lenvatinib [8], and radiation therapy [9]. These agents have shown promising results in preclinical and clinical studies, either alone or in combination with ICIs. For example, the combination of nivolumab and ipilimumab (a CTLA-4 inhibitor) with doxorubicin demonstrated significantly higher response rates and longer progression-free survival compared to nivolumab and ipilimumab alone in patients with advanced HCC [10].

There are also potential sensitizers that are currently under investigation for their efficacy in combination with ICIs in HCC treatment. These include other chemotherapy agents, such as gemcitabine and paclitaxel, and targeted therapies such as regorafenib and cabozantinib [11]. In general, current categories of those potential therapeutic approaches are (**Figure 1**):

1. MicroRNAs (miRNAs), are small non-coding RNA molecules that regulate gene expression and play important roles in various biological processes, including cancer development and progression. Several miRNAs have been identified as potential sensitizers for immune checkpoint inhibitors (ICIs) in HCC treatment, such as: (a). miR-34a: miR-34a is a tumor suppressor miRNA that can downregulate immune checkpoint molecules and enhance T-cell activation. Overexpression of miR-34a has been shown to sensitize HCC cells to PD-1 blockade therapy [12]. (b). miR-138: miR-138 is another tumor suppressor miRNA that can regulate immune checkpoint molecules and promote T-cell activation. Overexpression of miR-138 has been shown to enhance the antitumor effect of PD-1 blockade therapy in HCC [13]. (c). miR-200: miR-200 family members can inhibit the epithelial-mesenchymal transition (EMT) process and reduce the immunosuppressive tumor microenvironment. Overexpression of miR-200 has been shown to enhance the response to PD-1 blockade therapy in HCC [14]. (d). miR-142-5p: miR-142-5p can regulate the immune response by promoting T-cell activation and inhibiting regulatory T-cells. Overexpression of miR-142-5p has been shown to enhance the response to PD-1 blockade therapy in HCC [15]. (e). miR-155: miR-155 is a pro-inflammatory miRNA that can enhance the immune response to cancer cells. Overexpression of miR-155 has been shown to enhance the antitumor effect of PD-1 blockade therapy in HCC [16]. MiR-424 is also a candidate [17].

2. Chemotherapy agents: Chemotherapy can induce immunogenic cell death, which can enhance the immune response to cancer cells. When combined with ICIs, chemotherapy agents including HDAC inhibitor or CAXII inhibitor, can help to overcome tumor immune evasion mechanisms and improve response rates [7].

3. Targeted therapies: Targeted therapies that inhibit specific molecular pathways in cancer cells can enhance the efficacy of ICIs by reducing the immunosuppressive tumor microenvironment [18].

4. Toll-like receptor agonists: Toll-like receptor agonists can stimulate the immune system and enhance the antitumor activity of ICIs [19].

5. Cytokines: Cytokines such as interferon-gamma can promote immune cell activation and enhance the antitumor activity of ICIs [20].

6. Oncolytic viruses: Oncolytic viruses can infect and kill cancer cells, and also stimulate the immune system to enhance the antitumor activity of ICIs [1,2].

7. Epigenetic modulators: Epigenetic modulators can alter gene expression in cancer cells and promote the expression of tumor antigens, which can enhance the immune response to cancer cells [1,2].

8. Radiotherapy: Radiotherapy can induce immunogenic cell death and also enhance the immune response to cancer cells by promoting the release of tumor antigens[21].

9. Microbiota modulators: The gut microbiota can influence the response to ICIs, and modulators that alter the microbiota composition could enhance the efficacy of ICIs. Metabolic modulators such as metformin and statins can alter the metabolic profile of cancer cells and enhance the immune response to cancer cells [22].

The selection of proper sensitizers for ICIs in HCC treatment is crucial for improving patient outcomes. The ideal sensitizers should have a synergistic effect with ICIs, modulate the tumor microenvironment to promote an immune response, and have a favorable safety profile [1]. In addition, the future progress of selecting sensitizers, should be based on the specific molecular characteristics of the tumor and the patient, as well as the stage of the disease.

In conclusion, the discovery of proper sensitizers for ICIs in HCC treatment represents a significant breakthrough in the field of cancer

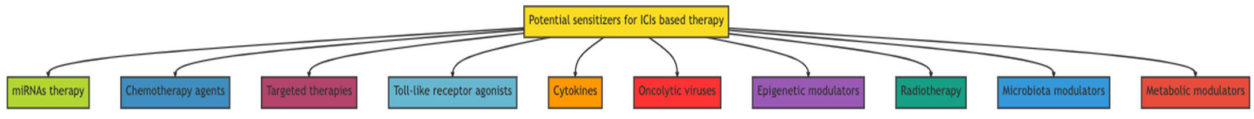

Figure 1. The different therapeutic approaches which can or might increase the therapeutic effect of ICIs base therapy for HCC.

therapy. Combination therapies with sensitizers have the potential to improve the overall response rates and survival outcomes for patients with HCC, overcoming the limitations of ICIs as a monotherapy. Existing sensitizers and potential sensitizers are promising, but we are still a long way from locating ideal combination for treating HCC, and totally understanding related mechanisms. Therefore, more research resources are encouraged to be invested in such field.

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