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Review Article

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Current Status and Future Direction of Immunotherapy in Hepatocellular Carcinoma: What Do the Data Suggest?

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Conflict of Interests
The authors declare no potential conflicts of interest.

Abbreviations
CI, confidence interval; FDA, Food and Drug Administration; HCC, hepatocellular carcinoma; HR, hazard ratio; ICI, immune checkpoint inhibitor; RECIST, Response Evaluation Criteria in Solid Tumors

ABSTRACT

Most patients with hepatocellular carcinoma (HCC) are diagnosed at an advanced stage of disease. Until recently, systemic treatment options that showed survival benefits in HCC have been limited to tyrosine kinase inhibitors, antibodies targeting oncogenic signaling pathways or VEGF receptors. The HCC tumor microenvironment is characterized by a dysfunction of the immune system through multiple mechanisms, including accumulation of various immunosuppressive factors, recruitment of regulatory T cells and myeloid-derived suppressor cells, and induction of T cell exhaustion accompanied with the interaction between immune checkpoint ligands and receptors. Immune checkpoint inhibitors (ICIs) have been interfered this interaction and have altered therapeutic landscape of multiple cancer types including HCC. In this review, we discuss the use of anti-PD-1, anti-PD-L1, and anti-CTLA-4 antibodies in the treatment of advanced HCC. However, ICIs as a single agent do not benefit a significant portion of patients. Therefore, various clinical trials are exploring possible synergistic effects of combinations of different ICIs (anti-PD-1/PD-L1 and anti-CTLA-4 antibodies) or ICIs and target agents. Combinations of ICIs with locoregional therapies may also improve therapeutic responses.

Keywords: Carcinoma, hepatocellular; Immune checkpoint inhibitor; Therapeutics

INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the most frequently diagnosed cancers and is a leading cause of cancer-related death. Cirrhosis induced by infection, such as by hepatitis B or C virus, is the principal cause of HCC. Other factors, *e.g.,* alcohol, drugs, autoimmune hepatitis, and non-alcoholic fatty liver disease are also associated with HCC development. The incidence of HCC is gradually increasing worldwide despite the development of potent antiviral agents (1-3). Chronic inflammation and subsequent fibrosis can induce the development of HCC; inflammation also results in increased tumor immunogenicity.

In the early stages of HCC, curative treatment is possible. However, 70%–80% of patients are diagnosed with advanced-stage HCC (4). Sorafenib is the first-line systemic therapy for