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Hepatocellular carcinoma in the era of immunotherapy

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ABSTRACT

Hepatocellular carcinoma is a common malignancy which usually emerges on a background of chronic liver disease. Unfortunately, with contemporary management, patients with advanced hepatocellular carcinoma have few treatment options, and prognosis is poor. The emergence of immunotherapy has afforded new therapeutic opportunities. This article reviews the clinical evidence for immunotherapy in advanced hepatocellular carcinoma and presents ideas for future drug development.

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Introduction

Hepatocellular carcinoma (HCC) is a leading cause of cancer-related morbidity and mortality. Relative to other malignancies, the incidence of HCC is fifth highest in men and ninth highest in women, and it accounts for the second most cancer deaths worldwide.¹ The continuing poor prognosis of HCC can be attributed to diagnosis at an advanced stage for which there remain few effective treatment options. Despite evaluation of a multitude of chemotherapy and targeted therapy agents, the only proven treatments for advanced disease are sorafenib, regorafenib, and lenvatinib,

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and overall survival benefits are modest. Clearly, there exists an unmet need for innovative approaches.

Immunotherapy has recently demonstrated activity in a number of malignancies. Building on this success, several immunotherapy trials have been undertaken in advanced HCC. The particular allure of immunotherapy in HCC is that it is mediated by viral hepatitis in many cases, and historically has been amenable to immune-based approaches such as interferon.

In this article, we highlight the preclinical and clinical evidence for immunotherapy in HCC. We begin with an overview of current practice, examine the rationale for introducing immunotherapy, then review current and prospective clinical trials. From this, we offer a perspective on future opportunities for advancing the role of immunotherapy in HCC.

Contemporary management

Early-stage HCC is usually treated with liver transplantation, surgical resection, ablation, or transarterial therapy, with the preference based on tumor extent, performance status, underlying liver function, and availability of donor organs. In contrast, there are few effective treatment options for advanced HCC, despite several decades of investigation into cytotoxic, hormonal, and targeted chemotherapeutics.

Sorafenib was the first agent to offer a survival benefit in advanced HCC. It is an oral multikinase inhibitor which inhibits growth and angiogenesis signalling pathways, including vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF). The efficacy of sorafenib was established in 2 large randomized controlled trials, the "Sorafenib HCC Assessment Randomized Protocol" (SHARP) study which was conducted in Europe and America,² and a similar study conducted in the Asia-Pacific region.³ Patients received either sorafenib 400 mg orally twice daily or placebo. Median overall survival (OS) improved from 7.9-10.7 months in the SHARP study, and from 4.2-6.5 months in the Asia-Pacific study, both statistically significant results. As a consequence, sorafenib has been the standard of care for first-line treatment of advanced HCC since 2008.

Another oral multikinase inhibitor, lenvatinib, was reported in 2017 conference proceedings to be noninferior to sorafenib.⁴ Patients received either lenvatinib 8-12 mg daily depending on body weight or sorafenib 400 mg orally twice daily. Median OS was 13.6 months with lenvatinib vs 12.3 months with sorafenib, fulfilling the prespecified noninferiority requirement. However, a greater proportion of patients receiving lenvatinib discontinued treatment due to adverse events (13% vs 9%). Further, patients with portal vein thrombosis were excluded, unlike the SHARP study with sorafenib, which limits the generalisability of findings to this worse prognosis group. Given the additional financial costs, the role of lenvatinib is therefore unclear.

Regarding second-line treatment of advanced HCC, the oral multikinase inhibitor regorafenib demonstrated survival improvement in the recent "Regorafenib for Patients With HCC Who Progressed on Sorafenib Treatment" (RESORCE) study.⁵ Patients who had progressed on sorafenib were randomized to either regorafenib 160 mg orally daily or placebo. The improvement in median OS from 7.8-10.6 months was statistically significant. This represented the first advance in the management of progressive HCC, with regorafenib likely to become a standard second-line option.

Notwithstanding the merit of these studies, the survival improvements from sorafenib, regorafenib, and lenvatinib have been modest, and the prognosis of advanced HCC remains dismal. Many other molecular targeted therapies and combinations have been evaluated without success, including sunitinib,⁶ erlotinib,⁷ brivanib,^{8,9} linifanib,¹⁰ vandetanib,¹¹ nintedanib,¹² dovitinib,¹³ axitinib,¹⁴ everolimus,¹⁵ codrituzumab,¹⁶ and ADI-PEG20.¹⁷ Others such as cabozantinib [NCT01908426] and ramucirumab [NCT02435433] remain under development. These findings have led to therapeutic stagnation in HCC, and highlight the need for an innovative treatment paradigm to improve outcomes.

Rationale for immunotherapy in HCC

Evasion of the immune system is now recognized as one of the hallmarks of cancer, key traits which are necessary for the transformation of normal cells into malignant cells and their ongoing

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