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Perspective

Advanced Hepatocellular Carcinoma and its Chronic Inflammation in Cancer Patients

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DESCRIPTION

Hepatocellular Carcinoma (HCC) is the most common type of liver cancer and a leading cause of cancer-related death worldwide. It usually occurs in the setting of chronic liver disease and cirrhosis, which result from chronic inflammation and fibrosis due to various etiologies, such as viral hepatitis (B or C), alcohol abuse, aflatoxin exposure, or metabolic disorders. The prognosis of patients with HCC is poor, especially for those with advanced disease that is not amenable to surgical resection, liver transplantation, or local ablation therapies.

Systemic therapy is the mainstay of treatment for patients with advanced unresectable HCC. However, until recently, systemic therapy options were limited and had modest efficacy and tolerability. Conventional cytotoxic chemotherapy agents have been shown to be ineffective and toxic for HCC patients, who often have underlying hepatic dysfunction and cirrhosis. Therefore, cytotoxic chemotherapy is no longer recommended by current guidelines for advanced HCC. In the past decade, there has been significant progress in the development of novel systemic therapies for advanced HCC, based on the improved understanding of the molecular pathogenesis and immunobiology of this heterogeneous tumor. These therapies include immunotherapy and molecularly targeted therapy, which aim to modulate the immune system or inhibit specific signaling pathways involved in HCC growth and angiogenesis.

Immunotherapy is a type of systemic therapy that harnesses the body's own immune system to fight cancer. It can be classified into two main categories: Immune Checkpoint Inhibitors (ICIs) and Adoptive Cell Therapy (ACT). ICIs are monoclonal antibodies that block the interaction between immune checkpoint molecules on tumor cells or immune cells, thereby enhancing the antitumor immune response. ACT involves the infusion of genetically modified or activated immune cells (such as T cells or natural killer cells) into the patient to directly attack tumor cells. Several ICIs have been approved or are under investigation for advanced HCC, such as nivolumab, pembrolizumab, atezolizumab, durvalumab, camrelizumab, and tislelizumab. These agents have shown promising antitumor activity and tolerability in various clinical trials, either as monotherapy or in combination with other agents (such as Tyrosine Kinase Inhibitors (TKIs), bevacizumab, or chemotherapy). However, not all patients respond to ICIs, and some may develop immune-related Adverse Events (irAEs), such as hepatitis, colitis, pneumonitis, or endocrinopathies.

ACT is still an experimental approach for advanced HCC, with limited data from early-phase trials. The main challenges of ACT include the selection of optimal immune cell sources and targets, the optimization of cell manufacturing and delivery methods, and the management of potential toxicities (such as cytokine release syndrome or neurotoxicity). Molecularly targeted therapy is another type of systemic therapy that inhibits specific molecules or pathways that are dysregulated or overexpressed in HCC cells, such as Vascular Endothelial Growth Factor (VEGF), Epidermal Growth Factor Receptor (EGFR), Fibroblast Growth Factor Receptor (FGFR), MET, RET, BRAF, MEK, PI3K/AKT/mTOR, Wnt/beta-catenin, and Notch.

Several TKIs have been approved or are under investigation for advanced HCC, such as sorafenib, lenvatinib, regorafenib, cabozantinib, sunitinib, linifanib, tivantinib, and ramucirumab. These agents have shown moderate antitumor activity and tolerability in various clinical trials, either as monotherapy or in combination with other agents (such as ICIs, bevacizumab, or chemotherapy). However, not all patients benefit from TKIs, and some may develop Adverse Events (AEs), such as hypertension, hand-foot-skin-reaction, diarrhea, fatigue, or hepatotoxicity.

CONCLUSION

Other molecularly targeted agents that are being explored for advanced HCC include monoclonal antibodies (such as bevacizumab), antibody-drug conjugates (such as rovalpituzumab

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tesirine), small molecule inhibitors (such as selumetinib), gene therapy (such as oncolytic viruses), and RNA interference therapy. The choice of systemic therapy for advanced HCC depends on several factors, such as the patient's performance status, liver function, tumor burden and characteristics, biomarker expression, prior treatment history, comorbidities, preferences, and availability of clinical trials. The optimal sequencing and combination of different systemic therapies are still under investigation. The current guidelines recommend a personalized and multidisciplinary approach to select the best systemic therapy option for each patient with advanced HCC.