

## REVIEW ARTICLE

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# Recent advances in the management of hepatocellular carcinoma

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## Summary

**Purpose:** The fifth most common cancer of the gastrointestinal system is liver cancer. It is also one of the most common cancers worldwide. The available treatment options include surgery, percutaneous ablation, and liver transplantation. Some of the latest modalities for the management of hepatocellular carcinoma (HCC) are radiofrequency ablation, trans-arterial chemoembolization, radioembolization and systemic targeted agents like sorafenib. The process of choice of a particular treatment modality in HCC depends on the tumor stage, patient performance status and liver function reserve. In the recent past with

progress in research, the short-term survival of HCC has improved but recurrent disease remains a fundamental problem as the pathogenesis of HCC is a multistep and complex process. The present review is focused on recent advances in the management of HCC. This review will also provide an insight on the upcoming latest modalities including the emerging role of hepatoma-derived growth factor (HDGF) overexpression in liver fibrosis and carcinogenesis.

**Key words:** hepatocellular carcinoma, hepatoma derived growth factor, management, target therapy

## Introduction

The third most common cause of cancer related deaths globally is due to HCC [1]. The widely accepted causes for this deadly condition include underlying liver diseases like hepatitis B and C, nonalcoholic steatohepatitis (NASH), hemochromatosis, autoimmune hepatitis, alcohol-related liver disease, primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC) [2]. Furthermore, the widespread utilization of surveillance programs in populations at risk is highly encouraged worldwide but still more than half of HCC cases are diagnosed late. On the other hand, curative therapies such as surgical resection, transplantation, or radiofrequency ablation are possible in fewer than 30% of the patients. Most of the HCC patients have unresectable disease at diagnosis [3,4]. The prognosis of patients with HCC is also poor,

and life expectancy is hard to envisage. Besides, there are reports suggesting that surveillance strategies in patients at a higher risk of HCC have led to the timely diagnosis of the disease, providing thus the chance of having much higher odds of curative response with the above different treatment options [5,6]. So, the available literature does not provide a concrete conclusion and reaching a certain decision is not easy.

This review will enlighten all the available as well as the most effective treatment modalities for the timely management of this deadly malignancy. Moreover, upcoming new strategies to tackle HCC both at clinical as well as preclinical stage will also be discussed. The review will benefit all concerned physicians, researchers and scientists working in the field in order to get better management of HCC.

## Molecular mechanics behind hepatocellular carcinoma

To accurately understand the latest modalities for the management of HCC, it is essential to first have some basic knowledge of the molecular basis of this disease. The core group of patients diagnosed with hepatitis B and C, alcohol abuse, metabolic syndrome, and aflatoxin toxicity are at great risk of advancing to HCC. So, the origin of HCC is diverse and hence, it is likely no one single genetic mutation or molecular pathway that functions as a crucial step is responsible for HCC tumorigenesis. But still, the hard work and continued dedication of biomedical research scientists have provided some important molecular pathways that are severely responsible for HCC genesis and evolution. The key mechanisms include :

1. Altered cell cycle regulation.
2. Aberrant angiogenesis.
3. Evasion of apoptosis.
4. Loss of intrinsic mechanisms to limit cell proliferation.

The above 4 basic mechanisms form the basis of the research to investigate specific genetic mutations related to loss-of-function mutations, altered methylation patterns, increased or decreased receptor activation, or telomere shortening, that somehow lead to the growth of HCC. Also, quite a few discrete signalling pathways have been recognized in the development and succession of HCC. The mainstream of these pathways involves the activation of protein kinases and their receptors. The in-depth knowledge of these molecules encouraged the focus of intense efforts at developing molecular targeted therapies for HCC.

## Current therapeutic modalities in use

### *Molecular target therapy*

The most common way to manage HCC is to target specific molecules responsible for the spread of this cancer. The prime molecule called vascular endothelial growth factor (VEGF) seems to be a primary mediator of angiogenesis in HCC as the tumor reported in HCC is one of the most vascular solid tumors [7]. Anti-angiogenic drugs such as bevacizumab (anti-VEGF antibody), and sorafenib (which acts in part to block the VEGF tyrosine kinase receptor) have proved their efficacy in blocking the above angiogenesis factor and are the prime choice of treatment in advanced

HCC cases [8,9]. Erlotinib is another small molecule inhibitor which targets the epidermal growth factor receptor (EGFR) tyrosine kinase in order to put control over angiogenesis. Furthermore, as combinations are the future of the war against cancer [10], a combination of the above two drugs, namely erlotinib and bevacizumab, was also studied in the recent past, yielding a median overall survival of 68 weeks, but was associated with gastrointestinal bleeding and fatigue [11].

### *Locoregional therapy*

The locoregional therapy was devised to minimize side effects associated with other therapies as it is directly localized to the tumor. It involves application of all available therapeutic procedures on the tumor itself, the only limitation being the tumor size, so it is not applicable in tumors larger than 4 cm. The common procedures involved are radiofrequency ablation (RFA), percutaneous ethanol ablation (PEI) and transarterial chemoembolization (TACE). RFA is a procedure in which part of the electrical conduction system of the tumor is ablated using the heat generated from high frequency alternating current (in the range of 350–500 kHz) [12]. The results and comparative studies conducted in the recent past supported the use of RFA over PEI as later it has been reported to have less recurrence-free survival rate of 77% at one year as compared to 86% offered by RFA [13,14]. On the other hand, TACE exploits rich blood supply of HCC. As liver normally has dual blood supply both from the hepatic artery as well as the portal vein, tumors derive blood preferentially from the hepatic artery. This therapeutic procedure is aimed to disrupt the rich blood supply of the hepatic tumor and is performed by injecting a chemotherapeutic agent such as doxorubicin or cisplatin suspended in a contrast medium such as lipiodol or gelfoam directly into the hepatic artery or arteries supplying the tumor. Moreover, TACE may also play a role in scaling down of tumors prior to surgery. In simple words, TACE is an established therapeutic protocol for HCC patients with unresectable disease, no vascular invasion or disease outside the liver.

## Advanced and upcoming therapeutic approaches against HCC

### *Radioembolization*

In the newer methods, radioembolization is the recent advancement in radiation therapy for HCC [15]. It basically involves utilization of mi-

crosspheres holding  $^{90}\text{Y}$  (Yttrium-90) beta-emitting radioisotope with a short half-life (2.67 days). These radioactive microspheres are injected through the hepatic artery; thereby they get trapped at the precapillary level, and selectively emit higher-dose radiation to the HCC [16]. The above mechanism limits the exposure of the surrounding normal liver parenchyma, thereby permitting higher dose delivery which is not possible with external radiation. Positive results confirmed the efficacy of radioembolization as median survival rates of the patients after the therapy was significantly higher [17,18]. The only precaution recommended for the above procedure is to check pulmonary shunt which ideally should be less than 20 % and is checked by  $^{99\text{m}}\text{Tc}$ -Macro aggregates along with angiography prior to the main procedure. Otherwise, there are prominent chances of misdelivery of  $^{90}\text{Y}$  to the gastrointestinal tract and that might reverse blood flow out of the liver [19].

#### *Beads assisted transarterial chemoembolization*

As discussed before, TACE is an efficient method utilizing the rich vascular supply of HCC. Beads-assisted TACE is the latest, innovative and much better version of TACE [20,21]. It involves utilization of embolic microspheres that have the ability to actively sequester the chemotherapeutic agent from solution and release it in a controlled fashion into the tumor. The main advantage of this method is the substantially diminished amount of the chemotherapeutic agent that reaches the systemic circulation and on the other hand it significantly enhances the local concentration of the drug and the antitumor efficacy [22]. The efficacy of advanced version of TACE has been reported recently [23-25]. Moreover, side effects like liver toxicity associated with standard TACE also declined significantly with beads-assisted TACE [26].

#### *Hepatoma-derived growth factor targeted therapeutic approach*

Hepatoma-derived growth factor (HDGF) is the latest target agent being explored for the

management of HCC [27]. It is a protein consisting of 240 amino acids isolated from the cultured supernatants of human hepatoma cell [28]. HDGF overexpression is involved in liver fibrosis and carcinogenesis. However, recently nucleolin (NCL) was identified and validated as a HDGF-interacting membrane protein in HCC. Moreover, it has been reported that NCL overexpression was correlated with tumor grades and vascular invasion in HCC patients. Hence, the latest evidence warranted the role of surface NCL and confirmed that it transmits the oncogenic signalling of HDGF. The latest finding opened gates to explore and investigate novel diagnostic and therapeutic agents based on HDGF in order to efficiently manage HCC patients.

#### *Chinese medicine (*Euphorbia helioscopia* L. extract) –upcoming approach for HCC*

In China, researchers are focused in exploring the newer therapeutic potential of traditional Chinese medicine, namely *Euphorbia helioscopia* L. extract for HCC. *Euphorbia helioscopia* L. is a herbaceous plant that is widely distributed in most parts of China and has been widely in use for the treatment of various pathological states like ascites, tuberculosis, dysentery, scabies, lung cancer, cervical carcinoma, and esophageal cancer [29,30]. However, there is a paucity of information with regard to its utility in HCC. Chinese researchers have utilized ethyl acetate extract (EAE) of *Euphorbia helioscopia* L. in a nude mice model of HCC and confirmed its capability to effectively reducing tumor growth, invasion and metastasis [31]. Moreover, it promoted apoptosis and significantly changed the ultrastructural morphology of xenografts. So, this study provided another upcoming option to be tried at clinical level for efficient management of HCC patients.

It is clear from the above review that the scientific society is operational on various possibilities for the timely and efficient management of HCC patients. The anticipations are high so as to study and develop new therapeutic approaches that can efficiently work in the clinical setting with least side effects to HCC patients.

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