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Perspective

Systemic treatment for hepatocellular carcinoma

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Abstract

Hepatocellular carcinoma (HCC) is one of the most common cancers with high mortality worldwide. Treatment options for patients with advanced stage HCC remain a great challenge. However, novel agents especially small molecule tyrosine kinase inhibitor and innovative immunotherapy demonstrate new promising therapeutic options for these patients. This review article summarizes systemic treatment options evaluated in HCC focusing on the most recently published data and ongoing studies.

Keywords: Hepatocellular carcinoma; Systemic treatment; Immunotherapy

Introduction

Liver cancer is the fifth most common cancer in men and ninth most common cancer in women worldwide.[1] Hepatocellular carcinoma (HCC) is the most common primary cancer of the liver (about 70%–85% of all liver cancers).[2] An estimated 42,220 new cases of liver cancer will be diagnosed in the United States in 2018.[3] The incidence rate of HCC is increasing in many parts of the world including the United States. The incidence rate increased by 3.1% per year from 2008 to 2012 and it is about 3 times more common in men than in women.[4]

HCC is an aggressive and lethal disease in general with the number of deaths per year close to its incidence worldwide.[5,6] The European Association for the Study of the Liver (EASL)–European Organization for Research on Treatment of Cancer (EORTC) Clinical Practice Guidelines report that HCC is a common cause of cancer-related deaths (692,000 cases), and accounts for 7% of all cancers throughout the world.[7] In the United States, the rate of HCC deaths appears to have increased by about 40% over the period 1990–2004, whereas the overall rate of cancer deaths has declined by about 18% during this same period. An estimated 30,200 liver cancer deaths will occur in the United States in the year 2018.[3]

HCC has a clear geographical distribution, with the highest incidence rates in East Asia and sub-Saharan Africa, where around 85% of cases occur.[8] This

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distribution pattern is considered to be reflective of the high prevalence of hepatitis B virus (HBV) infection and associated liver cirrhosis.[6] Worldwide, approximately 54% of HCC cases are attributed to HBV infection (which affects 400 million people globally) while 31% is attributed to hepatitis C virus (HCV) infection (which affects 170 million people), and approximately 15% is associated with other causes. Other important risk factors for HCC include heavy alcohol consumption, obesity, diabetes, and tobacco smoking.[7]

The diagnosis of HCC can be made by characteristic imaging studies without tissue biopsy which differs from a majority of other cancers that usually require a histological confirmation. HCC shows unique radiologic hallmarks such as hypervascularization in the arterial phase ("wash-in") followed by hypodensity at the portal venous phase ("wash-out"). The EASL panel of experts, the American Association for the Study of Liver Diseases (AASLD), Organ Procurement and Transplantation Network (OPTN), and American College of Radiology (ACR) Liver Imaging Reporting and Data System (LI-RADS) have proposed imaging criteria to diagnose HCC (nodule $\geq$10 mm).[7,9−11]

The current EASL−EORTC guidelines endorse the Barcelona-Clinic Liver Cancer (BCLC) classification that is followed by most clinicians. The BCLC includes prognostic variables related to tumor size, vascular/nodal invasion, distant metastasis, liver function and health performance status as summarized in Table 1.[12,13]

Various therapeutic options available for HCC include surgical resection, local ablative therapy or transarterial chemoembolization (TACE), radioembolization, radiation treatment and systemic treatment. In the very early stage and early stage, curative treatments such as liver resection, transplantation, or radiofrequency ablation have survival benefits. Local treatment including embolization, external beam radiotherapy (RT) and systemic therapy are the main treatment options for intermediate stage while systemic therapy is used for advanced stage.[14−16] Unfortunately, the role of radioembolization in locally advanced HCC treatment is debatable due to the recently reported negative data from the SorAfenib versus Radioembolization in Advanced Hepatocellular carcinoma (SARAH), selective internal radiation therapy versus sorafenib (SIRVENIB) and SORAfenib in combination with local MICro-therapy guided by gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid (Gd-EOB-DTPA) enhanced MRI (SORAMIC) studies.[17−19] Systemic treatment options for advanced HCC have been very limited historically, however, more novel treatments have become available in the past several years with promising new agents on the horizon. We are summarizing the HCC systemic treatments in this review (Table 2).[20−26]

First-line therapy

Sorafenib

Sorafenib acts by inhibiting multiple intracellular (c-RAF, BRAF, and mutant BRAF) and cell surface kinases [KIT, Fms-related tyrosine kinase (FLT)-3, rearranged during transfection (RET), RET/papillary thyroid carcinoma (PTC), vascular endothelial growth

Table 1
The BCLC classification.

Stage	Criteria
Very early HCC (BCLC stage 0)	Single tumor <2 cm in diameter No vascular invasion/satellites Patient has good health status (ECOG0) and well-preserved liver function (Child−Pugh A class)
Early HCC (BCLC stage A)	Single tumor >2 cm or 3 nodules <3 cm of diameter ECOG0 and preserved liver function (Child−Pugh class A or B)
Intermediate HCC (BCLC stage B)	Multinodular asymptomatic tumors without an invasive pattern, preserved liver function (Child−Pugh class A or B), ECOG 0
Advanced HCC (BCLC stage C)	Cancer related-symptoms (symptomatic tumors, preserved liver function, ECOG 1−2) Macrovascular invasion (either segmental or portal invasion) or extrahepatic spread (lymph node involvement or metastases)
Terminal HCC (BCLC stage D)	End stage liver function ECOG PS 3 or 4

BCLC: Barcelona-Clinic Liver Cancer; HCC: hepatocellular carcinoma; ECOG: Eastern Cooperative Oncology Group; PS: performance status.

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