Systemic Therapy for Hepatocellular Carcinoma and Cholangiocarcinoma

Vincent Chung, MD

KEYWORDS

• Hepatocellular carcinoma • Cholangiocarcinoma • Chemotherapy
• Molecular targets

KEY POINTS

- Hepatocellular carcinoma is the second most deadly cancer in the world.
- Sorafenib is the most active systemic therapy for hepatocellular carcinoma.
- Gemcitabine and cisplatin chemotherapy remains the standard treatment of cholangiocarcinoma.
- Significant progress has been made in understanding the signaling pathways that are important for carcinogenesis, leading to promising clinical trials.

SCOPE OF THE PROBLEM

The development of liver cancer is a growing problem worldwide. In the United States, the incidence rate increased by 4% from 2006 to 2010 and there will be an estimated 33,190 new cases in 2014.[1] Liver cancer can arise from hepatocytes leading to hepatocellular carcinoma or the intrahepatic bile duct leading to cholangiocarcinoma. The management of these patients requires a multidisciplinary team involving surgeons, gastroenterologists, radiologists, and oncologists in order to achieve the best outcome. This article reviews the chemotherapy treatment options.

HEPATOCELLULAR CARCINOMA

Introduction

Worldwide, hepatocellular carcinoma remains a significant problem with more than 745,000 people succumbing to the disease each year. This carcinoma is the second most deadly cancer behind lung cancer, with most cases occurring in east Asia and sub-Saharan Africa. In the United States, approximately 27,000 cases of hepatocellular carcinoma are diagnosed each year and the numbers are expected to increase.[1]

The author has nothing to disclose.
Department of Medical Oncology and Therapeutics Research, City of Hope, 1500 East Duarte Road, Duarte, CA 91010, USA
E-mail address: vchung@coh.org

Surg Oncol Clin N Am 24 (2015) 187–198
http://dx.doi.org/10.1016/j.soc.2014.09.009 **surgonc.theclinics.com**
1055-3207/15/$ – see front matter

The geographic variation of the disease is probably caused by the regional variation of exposure to hepatitis. In the Asian countries, hepatitis B is endemic with vertical transmission from parent to child. Aflatoxin, a mycotoxin produced by *Aspergillus flavus* and *Aspergillus parasiticus*, also plays a major role in developing countries. It commonly contaminates stored corn, peanuts, and soybeans in high-humidity areas and hepatocellular carcinoma often develops in younger individuals because of exposure at a young age. In the United States, most cases develop from hepatitis C or alcoholic cirrhosis resulting in cancer at a later age, and nonalcoholic fatty liver disease is a growing problem.[2]

Molecular Biology of Hepatocellular Carcinoma

Understanding the biology of the cancer is essential to help guide treatment. The development of cancer is a multistep process involving mutations of tumor suppressor genes or mutations leading to constitutive activation of signaling pathways. A complete discussion of the pathways is beyond the scope of this article but one of the most important pathways involved in hepatic carcinogenesis is the Ras/Raf/MAPK (mitogen-activated protein kinase) pathway.[3] Binding of epidermal growth factor, platelet-derived growth factor, or vascular endothelial growth factor (VEGF) to cell surface receptors leads to a signaling cascade activated by the Ras family of proteins (**Fig. 1**). Because of its importance in regulating cell proliferation, this pathway represents a potential target for therapy.

SORAFENIB

Sorafenib is a multikinase inhibitor that targets the serine-threonine kinase Raf-1 of the Ras/MAPK pathway in addition to having antiangiogenic properties. In the phase 1 clinical trial of sorafenib, 1 patient had an objective response by RECIST (Response

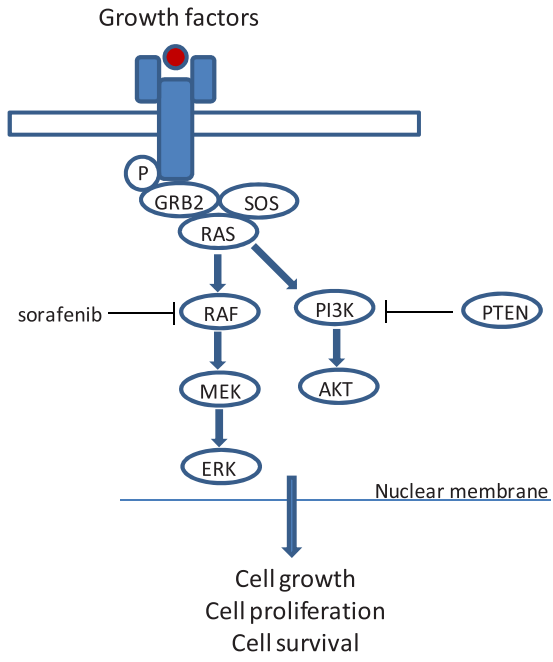

Fig. 1. RAS/RAF/MAPK signaling pathway. PI3K, phosphatidylinositol 3 kinase.