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Personalized therapy in hepatocellular carcinoma: Molecular markers of prognosis and therapeutic response

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ABSTRACT

Hepatocellular carcinoma (HCC) represents a growing worldwide health crisis with rising incidence, limited effective therapies and persistently poor prognosis. Five-year survival remains less than 20% despite decades of research. One byproduct of research efforts is the identification of numerous biomarkers of disease. From prognosis to therapeutic response, biomarker identification parallels a deeper molecular understanding of the disease that to date has generated limited gain in clinical outcomes. As one example, the classical prognostic biomarkers of tumor Ki-67 protein expression and *TP53* gene mutation have been repeatedly demonstrated to correlate with poor prognosis. There have been several studies throughout the past two decades identifying other gene-based biomarkers of prognosis. Critically, translation into the clinic has been slow and focus has shifted to a search for markers of therapeutic response in hopes of generating novel approaches to the disease. With this focus, many of the correlates are based on retrospective review of sorafenib effectiveness. Sorafenib, an oral targeted multi-kinase inhibitor, is currently the standard of care systemic agent for non-resectable disease. The Wnt-pathway, particularly when activated, is the most commonly cited molecular marker of sorafenib responsiveness. Additional work has identified a profile of genes involved in drug absorption, processing, and elimination that also appears to increase responsiveness. Overall, despite promising clinical data the use of biomarkers in the clinic for HCC is limited. In this piece, progress and opportunities for future work "beyond the genome" are highlighted, including metabolomic, epigenetic, and non-coding RNA studies. Additionally, barriers to the implementation of personalized therapeutic selection in HCC are reviewed.

Contents

Abbreviations: HCC, hepatocellular carcinoma; ICC, intrahepatic cholangiocarcinoma; PCNA, proliferating cell nuclear antigen; CIN, chromosomal instability; CDKI, cyclin-dependent kinase.

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1. Introduction

Hepatocellular carcinoma (HCC) arises from the hepatocytes and is the most frequently encountered primary liver malignancy. Common risk factors for HCC include conditions that cause persistent inflammation and scarring of the liver such as viral infection, alcoholic cirrhosis, and fatty parenchymal disease [1–3]. Chronic inflammatory conditions of the biliary tree, genetic disorders, and carcinogens can also increase the risk of developing HCC [3–5]. Common presenting signs in patients that develop HCC can vary based on tumor characteristics such as location and size. In the absence of screening programs for high-risk patients, indolent presentations can allow significant growth before symptoms occur. Consequently, discovery of disease at an advanced stage occurs among a large number of patients. The incidence of HCC in the United States approaches 40,000 patients per year, amounting to an epidemiologic rate of at least 8 per 100,000 individuals [1,3,6]. Of these individuals, historical data reveal that less than 20% will be alive at five years from the date of diagnosis [3]. The incidence of HCC is increasing at a rate that exceeds all but thyroid disease, and, together with ICC, HCC accounts for the largest annual percent increase in cancer death in the United States over the past two decades [1–4,6–8].

Contemporary management of HCC includes modalities directed at local and systemic disease control [9–11]. Currently, surgical extirpation is favored for HCC when technically possible. Options include hepatectomy and transplantation, depending on disease biology and patient comorbidities [12,13]. Other locally directed therapies include hepatic artery directed chemotherapy, radiotherapy, and ablative options [14]. External radiotherapy (whether by external beam or stereotactic body) can also be used in an attempt to achieve local disease control. Systemic cytotoxic chemotherapeutics in HCC have been trialed for decades in the setting of advanced disease with data demonstrating limited benefit [15,16]. Instead, the use of a molecular targeting agent, sorafenib, has demonstrated efficacy in patients with advanced disease and preserved liver function [17,18]. Although considered a targeted therapy, the use of sorafenib is somewhat indiscriminate, in that it is used without attempt at molecular characterization of the tumor. Despite contemporary multidisciplinary management, survival remains poor for patients with HCC, even when localized to the liver and resectable upon presentation [3].

An increasing understanding of cancer biology, in a variety of tumor types, has led to the discovery of various novel therapeutic agents over the past several decades. Beyond cytotoxic therapies, many solid tumors are now treated with combinations of hormonal, endocrine, or molecularly targeted agents, depending on the molecular characterization of an individual patient's tumor. For instance, molecular targeting is rapidly becoming standard for metastatic colorectal cancer demonstrating microsatellite instability [19,20]. This model of individualized patient care requires three key steps: reliable tissue sampling, accurate molecular characterization, and correlation of biomarkers with optimal therapeutic regimens. Reliable tissue sampling in HCC is rarely a burden as many tumors can be accessed via percutaneous or endoscopic means. In this article, we review the current understanding of molecular biomarkers in HCC and highlight the potential correlation with current and future therapies.

2. Molecular markers in hepatocellular carcinoma: prognosis

Hepatitis and cirrhosis are the principle causative factors leading to development of HCC. Additionally, alongside these inciting disease processes, research has enabled delineation of molecular markers involved in HCC prognosis and pathogenesis. More specifically, investigative efforts over the past two decades have allowed identification of genetic determinants of prognosis, as well as elucidation of biomarkers that play a role in hepatocyte proliferation, genome stability, cell cycle control, and apoptosis, among others [21]. Proposed molecular markers of prognosis in HCC may, in time, serve to supplement some of the hematologic based markers in practice today, such as alpha fetoprotein (AFP). AFP has been used to varying degrees to assist in diagnostic panels, assist in prognostic estimates, as well as monitor response to therapy [22–24]. AFP is not, however, used in the two most common staging systems for HCC (AJCC or BCLC staging systems). In addition, more recently, the utility of measuring the L3 fraction of alpha fetoprotein (AFP-L3) to aid in the diagnosis of HCC appears promising. AFP-L3 is a core fucosylated fraction of AFP and is generally reported as a percentage of total AFP; a level greater than 10% has been associated with the presence of advanced disease [25]. Finally, combining the measurement of AFP with other markers, such as prothrombin induced by the absence of vitamin K or antagonist-II (PIVKA-II), may improve the prognostic capacity of either marker alone [26]. For example, patients with increased AFP and increased PIVKA-II have a much worse prognosis than patients with lower levels of these biomarkers.

2.1. Histologic markers of prognosis

Classic molecular indicators of prognosis include the proliferative markers Ki-67 antigen and proliferating cell nuclear antigen (PCNA) [21,27]. Ki-67 is a protein that primarily aggregates in the nucleus and is present only in cells undergoing proliferation [28]. Cells in the resting state have no detectable Ki-67. In HCC, as well as other tumor types, Ki-67 is an important marker of tumor growth rate and poor prognosis [27,29,30]. Though preclinical tumor models demonstrate that silencing of Ki-67 protein arrests the cell cycle and proliferation, the actual molecular mechanism of Ki-67 remains elusive [31,32]. PCNA is another well-established marker of tumor proliferation and prognosis in HCC [33,34]. Although both Ki-67 and PCNA are powerful indicators of disease biology and prognosis, researchers have been unable to exploit this information for use in therapeutic targeting. Furthermore, despite evidence to support prognostic value in HCC, Ki-67 and PCNA testing is not routinely performed in many centers on specimens for HCC (See Tables 1 and 2)