Best Practice & Research Clinical Gastroenterology 28 (2014) 831–842

Contents lists available at ScienceDirect

Best Practice & Research Clinical Gastroenterology

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Integration of genomic information in the clinical management of HCC

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Keywords:
Hepatocellular carcinoma
Molecular profiling
Targeted therapies
Biomarker
Gene signatures

A B S T R A C T

Molecular profiling of hepatocellular carcinoma (HCC) is enabling the advancement of novel approaches to disease diagnosis and management. Accurate prognosis prediction in HCC is specially critical. Clinical staging systems for HCC support clinical decision-making (e.g., BCLC algorithm) might be complemented by molecular-based information in the near future. Molecular signatures derived from tumour and non-tumour samples are associated with patient recurrence an outcome. Single nucleotide polymorphisms have been linked with HCC development. Next generation sequencing studies have brought to light the genomic diversity of this disease. Gens recurrently altered in HCC and susceptible to be targeted belong to signalling pathways including telomere maintenance, cell cycle, chromatin remodelling, Wnt/beta-catenin, RAS/RAF/MAPK and PI3K/AKT/mTOR pathways. Oncogenic loops are unknown but might include some of the already discovered aberrations. Despite the intratumoral

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http://dx.doi.org/10.1016/j.bpg.2014.08.004

heterogeneity observed in HCC tumours, studies including large number of samples can identify key genetic drivers and contribute to the development of novel treatments and a personalized medicine.

Introduction

Liver cancer is the second leading cause of cancer-mortality and HCC is the 16th absolute cause of death world-wide, showing a steady increase in Western countries [1]. HCC accounts for 80% of all primary liver cancers world-wide. Most HCCs arise within a previously damaged liver, being chronic hepatitis (B and C) and alcohol abuse the main environmental causes for the underlying liver disease [2]. All these risk factors lead to chronic inflammation, hepatic fibrosis and eventually cirrhosis. Although surveillance programs for patients at-risk of developing HCC have improved significantly in the past years, less than 30% of patients are diagnosed at early stages when they are eligible for curative therapies such as resection, liver transplantation or local ablation [3]. Patients with intermediate stages benefit from chemoembolization and at more advanced stages benefit from the multikinase inhibitor sorafenib, which is the standard of care [4]. The SHARP clinical trial for sorafenib changed the landscape of clinical and translational research in the field, demonstrating the benefits of molecular targeted therapies. As is already the case for other types of cancers, accurate prediction of patient therapeutic response based on tumour molecular singularities will further improve overall efficacy of molecular therapies in HCC. On the other hand, prognosis prediction still relies exclusively on clinical parameters, and molecular data has not yet been integrated in the therapeutic decision-making algorithm and in the clinical management of HCC. Identification of biomarkers able to define subgroups of patients with dismal prognosis or high risk of HCC development will translate into better therapeutic strategies and allocation of resources. This review aims to describe the relevance of genomics in assessment of at-risk populations, diagnostic and prognostic tool in HCC, and to discuss which would be the benefits and limitations of integration of this molecular data into the existing HCC clinical algorithms.

Risk assessment of HCC: contribution of molecular profiling

Unlike other cancers, HCC usually arises on a previously damaged organ, being liver cirrhosis the underlying disease in more than 80% of cases. The annual incidence of HCC in cirrhotic patients is 3–5% [5] and one third of them will develop a tumour over their lifespan representing also the leading cause of death among them [3]. Environmental exposure, such as HCV or HBV viral infection, leads to chronic hepatic inflammation and increased potential for malignant transformation by facilitating genetic aberrations and cellular transformation, which is often referred to as 'field effect' [6]. In fact, severity of the underlying cirrhosis is correlated with increasing risk of HCC [7], especially in HCV-infected patients [8]. Even after complete surgical resection or local ablation of early HCC tumours, more than half of patients develop subsequent de novo tumours due to this cancer-prone microenvironment in the surrounding cirrhotic liver [3]. Thus, cirrhotic patients are an attractive target of HCC preventive intervention because at-risk individuals can readily be identified. However, the development of effective chemopreventive strategies in this population is hindered by the lack of a reliable understanding of the genomic sequence of events occurring in this premalignant milieu. The current understanding of the epidemiology of HCC defines some HBV-related factors (HBeAg positivity, high viral load, genotype C and HBV mutants) as independent predictors of HCC development [9,10]. Similarly, HCV genotype 1b was claimed to increase the risk of HCC development in a recent meta-analysis [11]. Aside of these clinical variables, the additional contribution of molecular biology would clarify the scenario for modern definition of at-risk populations, which will represent the main targets for chemopreventive drug assessment [12].