Hepatocellular Carcinoma: A Global Disease in Need of Individualized Treatment Strategies

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ASSOCIATED CONTENT

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Liver cancer incidence is increasing, with 782,000 new cases worldwide in 2012, more than 1 million cases per year projected by 2025, and a ratio of mortality to incidence close to unity, thereby suggesting a poor prognosis.[1] Hepatocellular carcinoma (HCC) represents nearly 90% of all primary liver cancers, and, typically, etiologic factors vary greatly by geographic regions around the globe. Indeed, a multifaceted portrait of HCC is rapidly emerging with several implications ahead, challenging clinicians in terms of public health measures and treatment strategies.

Whereas a significant reduction of hepatitis C virus (HCV) infections in Japan and hepatitis B virus infections in China have brought a decline in HCC, HCV infection rates in Oceania, Western Europe, and North America are steadily increasing. As a result, HCC trends in such historically low-risk areas are increasing, and HCC is now included among the more frequent causes of cancer-related deaths. Meanwhile, in Western countries, diabetes, obesity, and related nonalcoholic fatty liver disease, which are the hallmarks of the vast spectrum of metabolic syndrome, become more frequently recognized as risk factors for HCC[2] harboring distinctive clinical features from virus-induced counterparts.[3]

Regardless of its goals, curative or palliative, treatment of HCC is mainly stage driven, with the Barcelona Clinic Liver Cancer staging system being one of the most comprehensive tools. Nonetheless, other systems, such as the Hong Kong Liver Cancer system recently proposed, might be more appropriate and perform better, for example, in Asian populations where hepatitis B virus infection is still the predominant risk factor for HCC. Still, treatment recommendations also need to be tailored according to resource availability and to diverse health care systems capabilities.[4]

Given these premises, in this issue of *Journal of Oncology Practice*, Rich et al[5] provide a succinct but inclusive review on the management of HCC. In addition, they report on treatment modalities that perhaps are more peculiar to patterns of care observed within health systems of high-income countries, particularly the United States. In fact, the promising role of stereotactic body radiation therapy[6] now belongs to a context where current figures seem to have definitely outpaced the guidelines of most professional societies. This certainly mirrors an attitude shared by several institutions gauging risks and benefits of treatment options for the individual patient on the basis of more updated evidence, routinely discussed in the frame of multidisciplinary hepatobiliary tumor teams. Counterintuitive as they may seem to be, even the preliminary findings reported on early HCC recurrences after direct-acting antivirals against hepatitis C[7] reflect treatment strategies whose sustainability, again, would be questioned in many low-income countries. Clearly, for both liver stereotactic body radiation therapy and direct-acting antivirals, more robust

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data are much awaited before reaching firm conclusions on their right place in the management of HCC.

When it comes to the advanced-disease setting, a point perhaps not fully addressed by Rich et al[5] relates to possible approaches that need to be developed to individualize treatments, a relevant challenge in HCC. Evidence suggests that, similar to other oncology fields, a one-size-fits-all approach is not appropriate in HCC. Many data gained on clinical grounds hint at optimizing sorafenib therapy (or subsequent therapies), for instance, according to HCV status,[8] α-fetoprotein response[9] and α-fetoprotein levels, patterns of disease progression,[10] or reasons for sorafenib discontinuation.[10] As a matter of fact, because nearly 30% of patients eligible for second-line treatments permanently discontinue sorafenib as a result of an adverse event, a sound inclusion criterion of the Regorafenib After Sorafenib in Patients with Hepatocellular Carcinoma (RESORCE) study of regorafenib versus placebo was to limit the enrollment only to those patients who could tolerate sorafenib. From a clinician's standpoint, this strict criterion precludes any consideration about regorafenib efficacy in patients who cannot tolerate sorafenib but, not unexpectedly, it allows observation of a lower rate of treatment-related adverse events in patients receiving regorafenib.

Nevertheless, in managing patients with HCC, one of the major hurdles remains HCC heterogeneity, not only at the epidemiologic level but also at the molecular level. Because HCC is the only cancer type where a diagnosis can be determined in the absence of histologic confirmation, only a small proportion of patients with atypical imaging will ultimately undergo liver biopsy. However, the substantial lack of biologic specimens from the majority of patients with HCC, including those enrolled in most trials published thus far, has long hampered biomarker discovery in this disease. In this respect, although negative, the phase III METIV-HCC trial (ClinicalTrials.gov identifier: NCT01755767), by requesting a mandatory assessment of tumor mesenchymal-epithelial transition factor, was the first biomarker-driven trial and, hopefully, it has paved the way for a novel generation of clinical trials in HCC with biomarker-based enrichment strategies. JOP

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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