Commentary

Providing meaningful survival benefit to hepatocellular carcinoma patients: combination therapy of future

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Hepatocellular carcinoma (HCC) is a highly fatal disease, the mortality of which runs parallel to its incidence. Historically, viral hepatitis has been the major cause of HCC (1). Vaccine is available for hepatitis B virus (HBV) and a drug cocktail is effective in bringing down blood hepatitis C virus (HCV) level to zero. With successful application of mRNA vaccine for COVID-19, it is a matter of time before an effective vaccine for HCV is generated. Despite these positive advancements, the incidence of HCC is continuing to rise because of HCC development as a direct consequence of non-alcoholic steatohepatitis (NASH) caused by obesity (1). While viral hepatitis is waning in the Western countries, obesity is now a global problem, requiring impactful treatment regimen for HCC that can provide meaningful survival benefit.

The review paper by Zhang *et al.* discusses combinatorial treatments for advanced HCC (2). HCC at early stages, especially if the tumor is <5 cm in size, can be treated by transplantation, surgical resection in combination with radiofrequency ablation (RFA) and transarterial chemoembolization (TACE) (3). Historically advanced HCC was treated with a chemotherapy cocktail, and following a landmark clinical trial, angiogenesis-targeting strategy using a broad-spectrum tyrosine kinase inhibitor (TKI) sorafenib became the first-line treatment for HCC with subsequent introduction of newer generation of TKIs, such as lenvatinib. Similar to other cancers, immune checkpoint inhibitors (ICIs) are also showing promise for HCC, and anti-programmed cell death protein 1 (PD-1) monoclonal antibodies, such as nivolumab and pembrolizumab, have been approved for HCC treatment as a second line therapy following TKI therapy. Anti-PD-1 ligand-1 (PD-L1) monoclonal antibody (mAb), atezolizumab, and anti-vascular endothelial growth factor A mAb, bevacizumab, combination showed better efficacy than sorafenib alone, and was approved by FDA as a first line therapy for advanced HCC. As a consequence, multiple clinical trials are ongoing testing the combination of ICIs and anti-angiogenesis therapy, and Zhang *et al.* described in detail how to evaluate endpoints and properly interpret the findings to determine clinical response (CR), overall response rate (ORR) and overall survival (OS) in these clinical trials (2). The challenge of short follow-up period affecting correlation of efficacy and OS endpoint in phase III clinical trials was highlighted.

HCC develops after decades of chronic inflammation on a cirrhotic background which significantly compromises liver function. As such, use of broad-spectrum TKIs markedly increases treatment-induced toxicity severely affecting quality of life (QoL) thereby reducing patient compliance. The majority of the combinatorial clinical trials are testing combination of ICIs with a non-targeted

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drug. This is compounded by the observation that NASH-HCC patients respond poorly to ICI treatment compared to HCC patients with viral hepatitis (4). The focus needs to be shifted towards combining ICIs with gene-based therapy or small molecule inhibitors of specific driver oncogenes. Oncolytic vaccinia viruses showed promise in phase III clinical trials in HCC patients (5). Targeted nanoparticles delivering siRNA for an oncogene is another approach for tumors in the liver which is showing promise in pre-clinical studies and phase I/II clinical trials (6).

Zhang *et al.* mentioned that a definitive driver gene explaining the molecular mechanism of HCC has not been identified. However, molecular classification of HCC has identified sub-classes of HCC dependent on driver oncogenes (7). One example is MYC which is amplified in ~20% cases of HCC and can drive HCC development and progression on its own. A new generation of specific MYC inhibitors has been identified showing strong potency and synergism with ICI in multiple cancer indications in mouse models (8). These inhibitors are yet to be tested in HCC pre-clinical models, which might usher in new treatment regimens for a subset of HCC patients. In the spectrum of NASH to HCC, identification of genes that regulate both these processes allows development of preventive and therapeutic approaches. One such gene is AEG-1/MTDH which regulates lipid metabolism and inflammation on one end, and functions as a bona fide oncogene thus regulating the entire process (9). While selective AEG-1/MTDH inhibitors are being identified, targeted nanoparticle delivering siRNA for AEG-1/MTDH markedly inhibited both high fat diet (HFD)-induced NASH as well as HCC (9).

One important statistic that was highlighted by Zhang *et al.* is that 5-year survival rate for HCC patients in Japan is 50.4% which is markedly higher compared to that in the USA (10–15%), South Korea (18.9%) and Taiwan (20–22%) (2). This success was attributed to establishment of a nationwide surveillance program allowing early detection of the disease, and placing patients in curative treatment regimen, such as resection with RFA, TACE or hepatic artery infusion chemotherapy (HAIC) (10). With the raging obesity pandemic causing an alarming increase in NASH-HCC, it is mandated that nationwide early surveillance program, such as inclusion of abdominal ultrasound in annual health check-up especially in at-risk patients, needs to be established to effectively manage this fatal disease. The success of mammogram and colonoscopy in managing breast and colorectal cancers, respectively, further stresses this point. Identification of a specific blood biomarker for early HCC has huge potential for effective management of this highly virulent disease.

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Footnote

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