

# Hepatocellular carcinoma: expanding the horizon

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“Unfortunately, nature seems unaware of our intellectual need for convenience and unity, and very often takes delight in complication and diversity” Santiago Ramón y Cajal, Nobel Prize in Medicine 1906.

Hepatocellular carcinoma (HCC) is a major, increasing, public health problem in Asia. The estimated number of new liver cancer cases and liver cancer deaths in 2015 in China is 486,665 and 450,996, respectively (1). Because of differences in etiology, prognosis, staging systems used and treatment patterns, HCC is managed differently in Western and Asian nations (2). The new guidelines proposed by the expert panel led by Dr Shukui Qin (3), provide a useful specialized multidisciplinary care tool, which may help to improve efficiency when diagnosing and treating HCC patients.

In Eastern Asia the development of HCC is mainly related to chronic infection with the hepatitis B virus (HBV). We should remember that immunization against HBV infection is a cheap strategy to decrease the incidence of HCC (4). Since the strength of the evidence supporting the efficacy of surveillance programs in HBV infected patients in China is controversial (5,6), nomograms based on noninvasive clinical characteristics that may accurately predict the risk of HCC should be validated (7). Future diagnostic tools, such as a plasma microRNA panel (8), might allow the diagnosis of HCC at a very early-stage. In resected HCC patients, an association between survival and a recurrent gene-signature in non-tumorous liver tissue has been reported, opening the possibility of subsequent individualized therapies and a risk-adapted follow-up schedule (9).

The Barcelona Clinic Liver Cancer (BCLC) staging system offers a widely-accepted staging-guided treatment,

requiring only minor regional practice adaptations; notwithstanding, in some studies in both Western and Eastern populations, BCLC is suggested to be less accurate in predicting survival when compared with other currently used staging systems, particularly the Cancer of the Liver Italian Program (CLIP) (10,11). While most of these HCC staging systems take into account tumor biology and liver function, all of them fail to incorporate some major prognostic factors, such as microvascular invasion, for example, which is a fairly more important prognostic factor in surgically-resected HCC than other prognostic factors such as tumor size (12). New molecular prognostic factors, such as plasma levels of vascular endothelial growth factor (VEGF), could be integrated in currently used staging systems (13). Given that HCC is a heterogeneous disease, some molecular classifications of this tumor have been attempted and deserve to be clinically validated (14).

Technical improvements in locoregional therapies have expanded the number of HCC patients that are candidates for surgical resection, radiofrequency ablation and radiation therapy (RT). In patients with chronic liver disease, portal vein embolization before right hepatectomy reduces surgical morbidity and mortality. A novel two-step hepatic resection technique called “associating liver partition and portal vein occlusion for staged hepatectomy” (ALPPS) allows the two operations to be performed only one week apart (15). Recently published phase II clinical trials have shown that RT can be delivered in a safe and effective way, not only for palliative purposes but also for the treatment of early-stage HCC that is not eligible for curative therapies and as a bridge to liver transplantation (16). Several phase III randomized trials comparing RT versus (*vs.*) trans-arterial chemoembolization (TACE), RT plus TACE *vs.* TACE, and

sorafenib *vs.* RT (RTOG1112 trial) in patients with limited multifocal disease are currently ongoing.

Whether the novel and expensive catheter-based therapies using drug eluting beads (DEB) and yttrium-90 (<sup>90</sup>Y)-labeled microspheres are better than the classical TACE is an unresolved issue. Studies to clarify the optimal use of these techniques in terms of patient safety, efficacy, and cost-effectiveness are needed. The SPACE study (17) and the ECOG 1208 (18) are two ongoing randomized trials addressing the question of adding sorafenib to TACE and DEB-TACE, respectively. In the first study, sorafenib is administered continuously throughout the embolization period; in the latter one, sorafenib is temporally interrupted around the time of the embolization. The balance between safety and efficacy will determine which option is the best therapeutic strategy.

Since 2008, sorafenib remains the only systemic treatment that has proved to prolong survival compared with best supportive care in advanced HCC patients with compensated liver function. The cost of sorafenib for such a moderate benefit (less than 3 month improvement in median overall survival and no improvement in time to symptomatic progression), uncertain benefit in patients with Child B cirrhosis, and the lack of validated predictive biomarkers are some drawbacks of this therapy (19). Most of the targeted drugs under development are aimed at the inhibition of the angiogenic pathway; however, single agent anti-angiogenic therapies have reached an efficacy plateau. Many ongoing and planned trials combine molecularly targeted agents that inhibit different pathways or at different steps of the same pathway, usually at the expense of greater toxicities than expected for each drug alone (20). Combining targeted agents with chemotherapy is another rational strategy based on strong preclinical and clinical data (21); an ongoing phase III trial is currently evaluating the combination of sorafenib with doxorubicin *vs.* sorafenib alone.

In unselected advanced HCC populations, sunitinib and linifanib in the first-line therapy setting, and brivanib as second-line therapy, have failed to improve survival outcomes in three separate randomized trials that were recently reported (22). When developing new molecular-targeted agents, phase I clinical trials looking for the optimal biologic dose rather than the maximum tolerated dose, and biomarker-based randomized phase II clinical trials with time-to-event endpoints may contribute to maximize the likelihood of success in subsequent phase III trials. As an example, tivantinib, a very promising tyrosine

kinase inhibitor of the mesenchymal-epithelial transition factor (MET) receptor, was tested as a second-line therapy in a randomized phase II trial with a predefined biomarker analysis incorporated into the design, which concluded that this drug was not effective in patients with low expression of MET, but a pronounced benefit was observed in MET-overexpressing patients (23). More affordable drugs against advanced HCC than the current targeted drug therapies are urgently needed. Solid preclinical data support the clinical development of arsenic trioxide and traditional Chinese medicines in this setting.

Hopefully intensive research in this field will bring more accurate diagnosis and staging tools and more efficacious therapeutic options in the near future.

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