

# State of the Art – Hepatocellular Carcinoma

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Primary liver cancer (hepatocellular carcinoma, HCC) is the fifth most common cancer in men and the seventh in women worldwide.<sup>1</sup> It rarely occurs before the age of 40 years and reaches its peak incidence at approximately 70 years of age. Major risk factors for HCC include: infection with hepatitis B (HBV) or hepatitis C (HCV), alcoholic liver disease, non-alcoholic fatty liver disease and less frequently, hereditary haemochromatosis, primary biliary cirrhosis, alpha 1-antitrypsin deficiency or autoimmune hepatitis. Cirrhosis has the strongest association with HCC and is the most common known risk factor. HCC also occurs in non-cirrhotic livers in 10-15 % of cases with viral- and alcoholic-associated chronic liver diseases and in 40-60% of cases with non-alcoholic steatohepatitis (NASH).<sup>2,3</sup>

The Barcelona Clinic Liver Cancer (BCLC) staging system has been accepted worldwide in clinical practice and for many clinical trials. The American Association for the Study of Liver Diseases recommendations regarding liver transplantation (based on the Milan criteria) have not been changed in the 2011 update<sup>4</sup> because there are no new data which suggest any benefit in expanding these patient selection criteria. The utility of portal pressure measurement to define optimal candidates for major resection has been validated. Resection should therefore be the first-line approach in patients with normal portal pressure and bilirubin, even if studies of radiofrequency ablation (RFA) have demonstrated complete ablation of lesions <2 cm,<sup>5</sup> with low local recurrence rates of <1%.

The candidates for transarterial chemoembolisation (or TACE) include those with Child Pugh A or B liver function and intermediate (BCLC) stage B HCC, including patients with unresectable multinodular or large tumours. However, a greater standardisation of TACE techniques is needed. Recently, a new form of TACE (drug-eluting bead [DEB] with doxorubicin) has been developed to enhance tumour drug delivery and reduce systemic availability of conventional TACE. Particularly for patients with more advanced HCC and Child Pugh B, DEB is associated with improvements in 6-month tumour response (as measured by EASL) compared with conventional TACE.<sup>6</sup>

Patients who have either failed TACE or who present with more advanced HCC may benefit from sorafenib, a multikinase inhibitor. Sorafenib has been approved as the first-line treatment in patients with advanced HCC based on the results from the SHARP study.<sup>7</sup> Recent studies have also assessed the benefit of sorafenib as an adjuvant treatment or in combination with other techniques, such as TACE, to improve efficacy. This has dramatically heightened interest in the development of new treatments for HCC amongst previously reticent drug companies. There are now more than 50 phase I-III clinical trials evaluating targeted chemotherapies. Together, these studies might change the management of HCC and provide new combination therapies for intermediate as well as advanced HCC.

The use of selective internal radiation therapy (SIRT), also known as radioembolisation, in HCC is currently supported by retrospective or non-controlled studies.<sup>8,9</sup> These studies have shown that the median survivals with SIRT are similar to TACE and sorafenib, in BCLC B and BCLC C patients, respectively. Relevant clinical trials (SIRTACE, SORAMIC, SARAH) are now ongoing to determine the appropriate place of SIRT compared with TACE and targeted therapies in the treatment of HCC.<sup>10</sup>

A radiographic objective response to locoregional therapies (TACE or SIRT) using WHO or EASL criteria has recently been shown to predict survival in patients with Child-Pugh B7 or lower.<sup>11</sup> However, with low response rates to targeted therapies (only 2% of partial response according to RECIST criteria in SHARP study<sup>5</sup>), anatomical imaging using the RECIST criteria has become inappropriate. Instead magnetic resonance imaging (MRI) diffusion and computed tomography (CT) perfusion have enabled more accurate analysis of the vascular and interstitial compartments of the tumour after antiangiogenic therapy-. In addition, the concept of viable tumour (i.e. mRECIST criteria) defined as an uptake of contrast agent in the arterial phase of dynamic CT or MRI and the tumour density variations using CT<sup>12</sup> might also improve the analysis of tumour response with targeted therapies.

Finally, biomarkers have been recently characterised and provide additional tools in the evaluation of patients and the tailoring of treatment. Such surrogates may be of major interest to track the effect of antiangiogenic therapies, particularly in the case of stable disease: antiangiogenic agents may improve survival by slowing down tumour progression, without any obvious signs of tumor shrinkage or regression.<sup>7,13</sup> The identification of oncogenes that mediate tumour progression and trials that monitor their products as biomarkers, might lead to personalised therapies with optimal activity and cost benefit.<sup>14</sup>

Conflict of interest statement: The author has no conflict of interest

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**Figure 1.** Future multidisciplinary approaches for HCC treatment

