

# New Treatment Strategies for Hepatocellular Carcinoma

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## Q. Is anything changing in the use of surgery for the treatment of hepatocellular carcinoma?

Surgery is the basis for curing most epithelial tumors. For patients with hepatocellular carcinoma (HCC), the hope for cure is limited by late detection and a high chance of relapse due in part to the continuous carcinogenic activity in the diseased cirrhotic liver. Of course, the lack of drugs that can effectively eradicate micrometastasis also has a negative impact. We have recently learnt that biological markers like alpha-fetoprotein or the response to therapy can help select those patients with a less aggressive biological behavior and therefore less likely to harbor distant micrometastasis. Until recently, for instance, indication of liver transplantation in HCC was solely based on the amount of tumor burden. The integration of such biological markers in treatment algorithms would probably expand the benefit of resection or transplantation to patients with no so small or not so few tumors provided they have a good biology<sup>1</sup>. Several proposals are awaiting international validation but there is little doubt that some of them will transition to general clinical practice very soon.

## Q. Would that apply for liver resection as well?

For resection, the degree of liver dysfunction is as important as the amount and distribution of tumor burden. In cirrhotic livers, major and sometimes even minor hepatectomies can be contraindicated because of the risk of post-operative decompensation. This risk and the impact on long-term survival can now be better assessed based on the estimation of liver functional reserve with the ALBI (Albumin-Bilirubin) grade<sup>2</sup> or the MELD (Model for End Stage Liver Disease) score<sup>3</sup>, while intraarterial procedures can help increase the volume of the future liver remnant. Laparoscopic surgery, on the other hand, reduces post-operative morbidity. And finally, we also have to consider that the eradication of hepatitis C virus may well improve the regenerative ability even in the presence of established cirrhosis and will probably reduce the risk of *de novo* carcinogenesis. All these factors are now being shaped in new surgical strategies that have to be refined and validated.

## Q. New drugs have been approved in many countries. How are they changing practice?

The availability of more systemic therapies should change the field but so far, we have more prospects than realities. HCC is highly chemo-resistant and the multi-tyrosine kinase inhibitor (TKI) sorafenib was for many years the only drug shown to improve mortality of patients in the more advanced stages where locoregional therapies are not or no longer indicated<sup>4</sup>. Challenged again and again, no other oral multi-TKI has yet proven superior to sorafenib in this setting. We now have a second agent, lenvatinib, that is non-inferior to sorafenib in prolonging the survival of patients naive to systemic treatment and with a limited tumor burden<sup>7</sup>. Since they have slightly different side effects we can now tailor therapy in a more personalized way. However, and for reasons that are not clearly understood, the activity of sorafenib is restricted to those patients with fairly advanced tumors. When used in combination with TACE or following TACE, sorafenib failed to prolong time to progression or overall survival compared to placebo<sup>5</sup>. Furthermore, in patients with confirmed disease-free status after resection or percutaneous tumor ablation, sorafenib was unable to prolong time to recurrence again compared to placebo<sup>6</sup>. The lack of activity of other systemic agents that target

different pathways including epidermal growth factor receptor (EGFR), c-met or mTOR illustrate the lack of known oncogenic addiction in HCC. Therefore we have an unmet medical need here.

### **Q. Is the situation different in the second line?**

Over the last two years, three agents have shown positive results in randomized trials in the second line post-sorafenib. Regorafenib prolonged the survival of patients that were able to stably tolerate a relevant dose of sorafenib and progressed radiologically<sup>8</sup>. Cabozantinib prolonged the survival of patients that were intolerant or had progressed to up to two lines of systemic therapy including sorafenib<sup>9</sup>. And ramucirumab prolonged the survival of patients with serum AFP > 400 UI/ml who were intolerant or had progressed to sorafenib<sup>10</sup>. All these drugs share an antiangiogenic activity and differ in the spectrum of cell proliferation targets. Will these differences overcome the constraint of sorafenib in terms of activity across tumor stages? We don't know but it's unlikely that they will be tested as monotherapy given the poor results of sorafenib and their mechanism of action.

### **Q. Is immunotherapy the future in HCC?**

Immunotherapy has erupted in the field of liver cancer with the momentum gained in many other tumor types. The anti-PD-1 inhibitors nivolumab and pembrolizumab have been tested in single-arm trials. They consistently produce very durable objective remissions that are associated with long survival in around 15% of sorafenib-experienced patients<sup>11 12</sup>. This is excellent news. However, a note of caution is needed until we can analyze the results of randomized trials and see if the benefit involves a group of patients large enough to be captured in a randomized clinical trial with no patient selection based on patient or tumor characteristics. A recent press release reported that a trial comparing pembrolizumab versus placebo as second-line therapy after sorafenib failed to meet the two co-primary endpoints of overall and progression-free survival although both endpoints were significantly improved in the pembrolizumab-treated cohort. Another trial comparing nivolumab versus sorafenib as first-line therapy is expected to report results very soon.

In the meantime, based on the encouraging results and the scarcity of overlapping severe toxicities, a great variety of combinations are now under assessment in phase 2 and phase 3 clinical trials. This includes dual blockade of different immune checkpoint molecules or the combination of checkpoint inhibitors with the active multi-tyrosine kinase inhibitors, other antiangiogenics, or even drugs with unknown activity in HCC. Early data are available from two of these combinations, lenvatinib in combination with pembrolizumab<sup>13</sup> and bevacizumab in combination with the anti-PD-L1 inhibitor atezolizumab<sup>14</sup>. An encouraging 32% overall response rate using RECIST 1.1 criteria has been reported for the latter. Even more important, immune checkpoint inhibitors, alone and in doublets, are being tested in less advanced patients in combination with TACE and as adjuvant therapy after resection or ablation among patients at high risk of recurrence. But the field is not closed to other strategies and agents targeting fibroblast growth factor and TGF- $\beta$  are under investigation too. If confirmed, the availability of more potent systemic therapies able to induce durable and deep (even complete) tumor responses and equally effective against microscopic and macroscopic disease, will change the treatment of HCC and allow more patients to have grounds for a realistic hope of a cure.

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