

Moving beyond sorafenib alone in advanced hepatocellular carcinoma: is hepatic arterial infusion chemotherapy the best option?

Ikeda et al. recently published the results of an interesting randomized phase II trial comparing sorafenib alone with sorafenib plus hepatic arterial infusion chemotherapy (HAIC) with cisplatin in advanced hepatocellular carcinoma (HCC) [1]. The investigators reported an overall survival (OS) benefit for HAIC added to sorafenib, even though no significant advantage was reported in terms of time to progression (TTP) and response rate (RR). This combination strategy certainly represents an interesting approach in such a difficult setting and the findings justify further investigation in larger patient populations; however, some points deserve discussion in order to rationally design future clinical trials.

First, some imbalances between treatment arms may have influenced the OS results. Authors correctly commented on differences in the rate of hepatitis virus infection and portal vein tumour thrombosis (PVTT). Of note, also Barcelona Clinic Liver Cancer Group (BCLC) stage favoured the sorafenib-only arm. As a higher percentage of patients had hepatitis B virus-related disease (associated with poorer OS in advanced HCC), PVTT and BCLC-C stage in the combination arm, one could argue that the observed survival difference could have been even greater. However, as PVTT was an allocation factor, it is difficult to explain the imbalances observed for this parameter. As the sorafenib arm performed as expected in terms of RR, TTP and OS in Eastern populations [2], the reported survival difference for HAIC is worthy of note. Despite an apparently more extensive disease in the combination arm, more patients in the sorafenib plus HAIC arm received further loco-regional treatments such as HAIC, transarterial chemoembolization (TACE) or local ablation (53.8% versus 41.5%). As the inclusion criteria comprised unsuitability for TACE, the high rate of post-treatment TACE procedures may represent a potential bias in patient selection. Accordingly, was the OS difference the result of a median of 2 cycles of HAIC in first-line or the consequence of a more intensive management of a selected patient population?

The HAIC has been developed to increase the concentration of cytotoxic agents in the liver, thus maximizing the antitumor effect while reducing systemic toxicity of chemotherapy. Therefore, a minimal (if any) activity of such treatment on extra-hepatic disease should be expected. As only a trend for a RR advantage was observed in the combination arm, it could be of interest to evaluate objective response in the liver (excluding extra-hepatic sites), as well as TTP in the liver (as currently performed for other intra-hepatic therapies against liver metastases in different tumour types [3]). This analysis could shed light on how to select HCC patients for a

potentially useful procedure such as HAIC. This assumption is further supported by subgroup analysis, which found a greater OS advantage among patients with lower alpha-fetoprotein values.

Finally, the impact of the timing of HAIC relative to sorafenib therapy deserves further analysis. Since sorafenib may act as a sensitizer and synergistic compound with cisplatin as well as exerting antiangiogenic activity in the tumour, duration of sorafenib treatment before HAIC could have an influence on clinical outcomes in terms of RR or TTP.

To conclude, the paper by Ikeda et al. certainly represents a step forward in the direction of integrating loco-regional procedures with sorafenib in the management of advanced HCC. However, a definitive answer to whether HAIC is the right path towards improved outcome and how it compares with other promising techniques (such as transarterial radioembolization [4]) in this setting is yet to come.

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