Editorial

Regorafenib for hepatocellular carcinoma progressing on sorafenib: just another starting point

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Hepatocellular carcinoma (HCC) is the second most common cause of death from cancer worldwide and a major global health problem. The incidence of HCC increases progressively with advancing age, reaching a peak at 70 years. Moreover, there is a growing incidence of HCC worldwide (1).

Cirrhosis of whatever etiology is an important risk factor for HCC and about one-third of cirrhotic patients will finally develop HCC during their lifetime. Moreover, HCC generally arises in the context of cirrhosis. Consequently, liver transplant (LT) is nowadays the only treatment able to remove at once both the seeded-HCC and the damaged-hepatic tissue in which cancerogenesis and chronic liver disorders have together progressed (2).

Apart from LT, the only cure of both HCC and underlying liver cirrhosis, all the other treatments have to match with higher rate of HCC recurrence. The latter can be classified into curative and palliative treatments. However, these treatments, often used as a bridge for LT, are shown to be effective in terms of survival without cancelling the possibility of HCC recurrence due to the underlying liver cirrhosis. Unfortunately, in a significant amount of cases, HCC is advanced and unsuitable for LT or other curative treatments (3).

Management of advanced HCC has been challenging for physicians for years, particularly for patients who are only suitable for systemic therapy (1,3). The demonstration that sorafenib significantly prolongs survival for advanced HCC has opened new avenues of research. However, albeit having long been the only therapy able to improve the outcome of advanced HCC, due to the presence of underlying liver cirrhosis, the benefit of sorafenib is only limited to patients with adequate liver function and the gain in terms of survival is of only about 3 months (4,5). Moreover, the enthusiasm for further promising treatment has long been discouraged by the fact that almost all the potentially second line therapies after sorafenib systematically failed to improve survival in clinical trials (6-14). Some consideration is needed about the long wait of an effective second line treatment for HCC after sorafenib failure. This difficulty probably reflects the complexity of treating HCC due to the underlying liver cirrhosis, encountered not only by researchers but, also and mostly, by physicians in everyday clinical practise. In fact, despite the evidence of sorafenib efficacy for advanced HCC, the use of sorafenib has not spread, mostly due to the concern of managing both possible sorafenib adverse effects and complication of underlying cirrhosis. Consequently, the same limited spread of treatment will likely be an issue also for second line therapies.

Finally, a recent multi-center randomized double-blind placebo-controlled phase 3 trial comparing best supportive care plus regorafenib or placebo for HCC progressing on sorafenib, enclosing 567 patients (374 regorafenib versus 193 placebo), reported a significantly improved survival for regorafenib (median survival 10.6 versus 7.8 months, $P<0.0001$). Adverse events were reported to be similar to those described for sorafenib and did not significantly affect survival. Authors correctly concluded that regorafenib is the only systemic treatment shown to provide survival benefit in HCC progressing on sorafenib treatment. Overall, the trial was well designed ad results are

convincing and relevant (15). However, as well as for those generally considered for sorafenib, the inclusion criteria limited the study to only patients with adequate liver function (Child Pugh class A). Furthermore, the study excluded patients who discontinued sorafenib because of adverse events. In fact, due to the similar range of adverse events, it is probable that patients with significant adverse events on sorafenib would not have benefit with regorafenib. Consequently, following this indication, in clinical field practise, most of HCC progressing on sorafenib would not be suitable for treatment with regorafenib because of both liver function deterioration or previous sorafenib adverse events. Furthermore, net of these stringent selection criteria, the gain of regorafenib in terms of survival seems to be of about only 3 months (15).

The results of the present trial are important, but the performance of regorafenib as second line therapy needs to be confirmed in field practise, especially in patients with other comorbidities. In fact, the experience with sorafenib raises the concern of substantial drug to drug interaction, in particular in clinical settings characterized by the need of different concomitant multiple drug exposure (16-20).

Pragmatically, the recent evidence of regorafenib efficacy for HCC progressing on sorafenib opens two different clinical scenarios. The former is a step by step consecutive strategy in which sorafenib is the first treatment option followed by regorafenib once HCC progression on sorafenib occurs. The latter is the perspective of exploring, in future clinical trials, a multidrug therapy in which regorafenib is used together with other systemic agents. Both the strategies would have the limitation linked to patients' selection, potentially including only patients with advanced HCC in cirrhosis with adequate hepatic function and without previous history of sorafenib adverse events. Furthermore, the latter strategy should be explored with caution due to the concern of adverse events potentially correlated to drug to drug interaction, an issue already reported for sorafenib in different clinical contexts (16-20).

Unfortunately, despite the good news of the possibility of treating with regorafenib advanced HCC progressing on sorafenib, with the evidence of a further, albeit limited, improvement of survival, the way to optimize the therapy of advanced HCC still appears uphill and the current therapeutic armamentarium far from perfect.

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