Towards a tailored systemic therapy for liver cancer

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Hepatocellular carcinoma (HCC) is the fifth most frequent malignancy and the leading source of mortality in cirrhotic patients (1).

In spite of the latest advancements in diagnosis and screening campaigns in cirrhotic subjects, a majority of patients are still diagnosed in advanced stage and they are not amenable to curative radical treatments such as surgery, orthotopic liver transplantation (OLT), or radiofrequency ablation (RFA) (2,3).

Sorafenib (Nexavar®, Bayer, Leverkusen, Germany), an oral multikinase inhibitor, constitutes the first-line systemic treatment in advanced HCC patients unsuitable to radical or loco-regional therapies (2-4). In particular, sorafenib determined a significant survival benefit both in patients refractory to other therapies (“post-progression survival” benefit) (5,6) and in subjects who could not be treated with surgery or loco-regional therapy (2-4,7-9), while the benefit in the adjuvant setting after resection or RFA was challenged in a landmark multicenter randomized-controlled trial (RCT) (10-12).

However, the lack of effective second-line agents able to significantly impact treatment outcomes after tumor progression or in subjects intolerant to sorafenib has paved the way to intense research with several chemotherapeutic agents tested in this field, unfortunately mostly with disappointing results (13,14).

Among the tested agents, regorafenib (Stivarga®, Bayer, Leverkusen, Germany) was found to lead to a median overall survival (OS) of 11.08 months [95% confidence interval (CI), 9.46–12.71] and median progression-free survival (PFS) of 3.24 months (95% CI, 2.68–3.86) in second-line setting after sorafenib in a meta-analysis of 8 studies (15). However, the limited efficacy and the narrow therapeutic window (similar to sorafenib treatment), prompted to test other agents, preferentially targeting other molecular pathways.

Axitinib (Inlyta®, Pfizer, New York, USA) is a potent and selective inhibitor of vascular endothelial growth factor receptors (VEGFRs) 1-3, approved for treatment of second-line metastatic renal cell carcinoma (16). Based on these premises, a global randomized phase II study did not find a significant OS benefit as compared to placebo/best supportive care (BSC) in second-line HCC patients, while improvements favoring the axitinib/BSC arm were observed in PFS, especially among Asian patients (17).

In an interesting manuscript recently published in Liver Cancer, Kudo et al. analyzed data from the aforementioned trial (17) with the aim to explore the efficacy and safety of axitinib based on location of recruitment (Asia versus non-Asia versus Asian subgroups) and to investigate the potential predictive and/or prognostic value of baseline levels of circulating microRNAs (miRNAs) and serum soluble proteins thus attempting to explore the predictive role of several molecular biomarkers (18).

In this series of 202 patients, 78 non-Asian and 124 Asian, no significant differences in OS were found according to location of enrollment. However, in an exploratory analysis excluding patients intolerant to prior antiangiogenic therapy, axitinib showed favorable OS in Asians, especially Japanese patients (18). No difference in safety profile was observed on regional basis. Four circulating microRNAs, including miR-5684 and miR-1224-5p, and stromal cell-derived factor 1 were found to play a predictive role in both Asians and non-Asians (18).
Therefore, the authors concluded that axitinib may represent a valuable option in a subgroup of Japanese patients that excludes sorafenib-intolerant subjects; moreover, several potential biomarkers might help the clinician in selecting a subgroup of patients more likely to benefit from axitinib therapy (18).

As there was an imbalance in geographic representation of enrolled patients, the subgroup analysis conducted on regional basis should be interpreted with caution and further large RCTs enrolling an adequate number of Western patients are warranted in order to confirm these results.

Furthermore, the real impact of treatment-related adverse events (AEs) on patient survival should be deeply explored as several studies attest the relationship between AEs, especially dermatological ones, and OS in HCC patients treated with sorafenib (19-22).

It is our opinion that, given the disappointing results of axitinib in the preliminary phase-II trial (17), the forthcoming research should be focused on other pharmacological agents targeting other pathways. Unfortunately, the current state-of-art and the growing amount of negative trials seem to speak against the current pharmacological agents in HCC patients non-responsive or intolerant to sorafenib (23).

On the other hand, the most interesting finding of this study is the predictive role of several biomarkers, which might be of interest also with other chemotherapeutic agents in HCC patients (24).

In conclusion, although axitinib is unlikely to change the therapeutic landscape in hepatono-cology, the study by Kudo et al. (18) further strengthens the concept of the importance of subgroup post-hoc analysis and the predictive role of biomarkers in HCC patients. This approach should be considered in all the RCTs testing novel therapeutic agents in order to deliver a more precise oncology tailored on the molecular characteristics of each single patient.

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References

1. El-Serag HB. Hepatocellular carcinoma. N Engl J Med 2011;365:1118-27.
2. Galle PR, Forner A, Llovet JM, et al. EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. J Hepatol 2018;69:182-236.
3. Heimbach JK, Kulik LM, Finn RS, et al. AASLD guidelines for the treatment of hepatocellular carcinoma. Hepatology 2018;67:358-80.
4. Llovet JM, Ricci S, Mazzaferro V, et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 2008;359:378-90.
5. Reig M, Rimola J, Torres F, et al. Postprogression survival of patients with advanced hepatocellular carcinoma: rationale for second-line trial design. Hepatology 2013;58:2023-31.
6. Facciorusso A, Del Prete V, Antonino M, et al. Post-recurrence survival in hepatocellular carcinoma after percutaneous radiofrequency ablation. Dig Liver Dis 2014;46:1014-9.
7. Citterio D, Facciorusso A, Sposito C, et al. Hierarchic Interaction of Factors Associated With Liver Decompensation After Resection for Hepatocellular Carcinoma. JAMA Surg 2016;151:846-53.
8. Rognoni C, Ciani O, Sommariva S, et al. Trans-arterial radioembolization in intermediate-advanced hepatocellular carcinoma: systematic review and meta-analyses. Oncotarget 2016;7:72343-55.
9. Sacco R, Antonucci M, Bresci G, et al. Curative therapies for hepatocellular carcinoma: an update and perspectives. Expert Rev Anticancer Ther 2016;16:169-75.

10. Bruix J, Takayama T, Mazzaferro V, et al. Adjuvant sorafenib for hepatocellular carcinoma after resection or ablation (STORM): a phase 3, randomised, double-blind, placebo-controlled trial. Lancet Oncol 2015;16:1344-54.

11. Facciorusso A, Muscatiello N, Di Leo A, et al. Combination therapy with sorafenib and radiofrequency ablation for hepatocellular carcinoma: a glimmer of light after the storm trial? Am J Gastroenterol 2015;110:770-1.

12. Cabibbo G, Tremosini S, Galati G, et al. Transarterial chemoembolization and sorafenib in hepatocellular carcinoma. Expert Rev Anticancer Ther 2014;14:831-45.

13. Facciorusso A, Licinio R, Carr BI, et al. MEK 1/2 inhibitors in the treatment of hepatocellular carcinoma. Expert Rev Gastroenterol Hepatol 2015;9:993-1003.

14. Sacco R, Bargellini I, Ginanni B, et al. Long-term results of sorafenib in advanced-stage hepatocellular carcinoma: what can we learn from routine clinical practice? Expert Rev Anticancer Ther 2012;12:869-75.

15. Facciorusso A, Abd El Aziz MA, Sacco R. Efficacy of Regorafenib in Hepatocellular Carcinoma Patients: A Systematic Review and Meta-Analysis. Cancers (Basel) 2019;11:2346.

16. Gross-Goupil M, Kwon TG, Eto M, et al. Axitinib versus placebo as an adjuvant treatment of renal cell carcinoma: results from the phase III, randomized ATLAS trial. Ann Oncol 2018;29:2371-8.

17. Kang YK, Yau T, Park JW, et al. Randomized phase II study of axitinib versus placebo plus bestsupportive care in second-line treatment of advanced hepatocellular carcinoma. Ann Oncol 2015;26:2457-63.

18. Kudo M, Kang YK, Park JW, et al. Regional Differences in Efficacy, Safety, and Biomarkers for Second-Line Axitinib in Patients with Advanced Hepatocellular Carcinoma: From a Randomized Phase II Study. Liver Cancer 2018;7:148-64.

19. Díaz-González Á, Sanduzzi-Zamparelli M, Sapena V, et al. Systematic review with meta-analysis: the critical role of dermatological events in patients with hepatocellular carcinoma treated with sorafenib. Aliment Pharmacol Ther 2019;49:482-91.

20. Ponziani FR, Bhoori S, Germini A, et al. Inducing tolerability of adverse events increases sorafenib exposure and optimizes patient’s outcome in advanced hepatocellular carcinoma. Liver Int 2016;36:1033-42.

21. Sacco R, Granito A, Bargellini I, et al. Clinical outcomes with long-term sorafenib treatment of patients with hepatocellular carcinoma: a multicenter real-life study. Future Oncol 2018;14:3049-58.

22. Cabibbo G, Rolle E, De Giorgio M, et al. Management of cirrhotic patients with hepatocellular carcinoma treated with sorafenib. Expert Rev Anticancer Ther 2011;11:1807-16.

23. Sacco R, Misms V, Romano A, et al. Assessment of clinical and radiological response to sorafenib in hepatocellular carcinoma patients. World J Hepatol 2015;7:33-9.

24. Sacco R, Misms V, Granito A, et al. Correlation between LDH levels and response to sorafenib in HCC patients: an analysis of the ITA.LI.CA database. Int J Biol Markers 2015;30:e65-72.

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