Received: 24 October 2023 | Accepted: 25 October 2023

DOI: 10.1111/liv.15781

Liver INTERNATIONAL WILEY

EDITORIAL

May we actually help clinicians select the best systemic treatment for patients with intermediate-stage hepatocellular carcinoma?

Systemic treatment of patients with hepatocellular carcinoma (HCC) has shifted from being indicated almost exclusively in those with advanced stage to encompass also patients with intermediate stage, according to the Barcelona clinic liver cancer (BCLC) staging system.[1] This treatment migration towards an earlier stage of disease is mainly a consequence of the encouraging results reported in registration trials of newer treatments, including lenvatinib and atezolizumab/bevacizumab, where median objective response rates of 24.1% and 30.0%, and median overall survival of 13.6 and 19.2 months, respectively, were observed.[2,3] These results stimulated an interest in treating also patients with intermediate-stage HCC who were unlikely to respond to trans-catheter arterial chemo-embolization (TACE), the 'conventional' treatment suggested for this stage.[4] As a fact, lenvatinib demonstrated higher objective response rate and longer overall survival, as compared to TACE, in patients with intermediate-stage HCC who were beyond the up-to-seven criteria.[5] Furthermore, both lenvatinib and atezolizumab/bevacizumab have been used in patients unsuitable for TACE, also in an attempt to downstage the cancer and eventually enable curative treatments.[6,7]

As both lenvatinib and atezolizumab/bevacizumab are used in clinical practice as first-line systemic therapies for patients with unresectable HCC, in the current issue of Liver International Tada et al. report the results of a large, multicentre, retrospective study aimed at evaluating some oncological landmarks such as progression-free survival, overall survival and radiological response in patients with intermediate-stage HCC who were deemed unsuitable for TACE and received either lenvatinib or atezolizumab/bevacizumab.[8] Their aim was to provide physicians an initial piece of evidence to support clinical decisions in this setting, considering the absence of direct comparative studies between the two treatment regimens. They showed similar overall survival and objective response rates in patients treated with lenvatinib and atezolizumab/bevacizumab. This latter group showed increased progression-free survival as compared to the group treated with lenvatinib, considering both unselected and propensity score-matched patients.[8] Adverse events, and severe adverse events, were present in both two treatment groups, segregating as expected from the registration clinical trials.[2,3,8]

Retrospective comparison of two treatment regimens cannot be regarded as the highest evidence to support a clinical decision, and although Tada et al. performed a propensity score-matched comparison to account for differences in the two populations, propensity scores cannot account for unmeasured confounding that might have influenced treatment decisions, thus biasing the study results.[8,9] However, from a practical point of view, this study provides indirect information in a future scenario where these medications will be increasingly used.[10,11] In fact, patients with BCLC intermediate stage represent almost one out of seven patients with HCC, and little evidence is available to guide the overall management with systemic therapy of this large share of patients.[12] Basing their assumption on the results of a study that identified a correlation between progression-free survival and overall survival in patients with HCC treated with systemic therapies, the authors support the use of atezolizumab/bevacizumab rather than lenvatinib as initial approach in patients with intermediate-stage HCC, in particular in those who are deemed unsuitable for TACE.[8,13] The authors need to be commended for explicitly stating criteria contraindicating TACE in the intermediate-stage patients studied. Interestingly, the latest American Association for the Study of Liver Diseases guidance on HCC management also defines a number of factors that contribute to unsuitability for trans-arterial treatments.[14] Unfortunately, however, the authors did not report overall survival figures in the subsets of intermediate-stage patients where systemic treatment, rather than TACE, may make the difference such as Child-Pugh class B patients and those with an albumin-bilirubin grade ≥2, where progression-free survival was not different between the two treatments, and where overall survival with systemic treatment is particularly grim.[15,16]

From the patient perspective, when dealing with therapy of an advanced cancer with a low likelihood of definite cure, as the population included in this study, the main questions are whether the proposed treatment will help them live longer and whether this will be compatible with a good quality of life.[16] The first piece of information we can glean from the real-world study of Tada et al. is that, even in patients with unfavourable liver-related and oncological features, treatment with either lenvatinib or atezolizumab/bevacizumab is associated with overall survival figures that are meaningfully longer than those reported in well-selected patients enrolled

in registration trials (lenvatinib 20.6 vs. 13.6 months; atezolizumab/bevacizumab 24.0 vs. 19.2 months).[2,3,8] Likewise, despite the limitations related to the absence of centralized, masked assessment of radiological response, it seems that also the rate of objective response was higher in this study than in registration trials in both lenvatinib- (47.2% vs. 24.1%) and atezolizumab/bevacizumab-treated patients (49.4% vs. 30.0%). Unfortunately, besides reporting the rates of adverse events, this study does not provide a definite information regarding both patients' quality of life and preference on the two regimens, thus leaving this relevant question unanswered.

In summary, patients selected to undergo treatment with atezolizumab/bevacizumab show a better progression-free survival than those selected for treatment with lenvatinib, a finding confirmed also by propensity score matching. However, these results should be interpreted with caution due to conceptual and practical reasons. Firstly, progression-free survival rate takes into account both progression and death as a combined end point, and while the relevance of this end point is questionable from the oncological point of view, the criticism is even more cogent in patients with HCC where death may occur from liver failure independently of oncological progression.[17–20] Unfortunately, in the study by Tada et al. causes of death were not reported.[8] Moreover, we are also unable to assess whether the similar overall survival rates of patients treated with either regimen were supported by second-line treatments following progression, or conversely to a shift to more efficacious treatments in patients showing excellent response to either lenvatinib or atezolizumab/bevacizumab as also these data were not reported.[8] In the absence of these data, the lack of difference in overall survival in front of clearly better progression-free survival remains puzzling, and therefore—lacking direct comparisons—the selection of systemic treatment for patients with intermediate-stage HCC will likely depend more on the perception by treating physicians of subtle clinical differences in patients profiles, and on patients' preference, while waiting for adequately powered studies that will show us which treatment regimen is actually associated with prolonged overall survival and improved patients' quality of life.

CONFLICT OF INTEREST STATEMENT

Edoardo G. Giannini advises for AstraZeneca, Roche, Eisai and MSD. Mario Strazzabosco advises for Engitix.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no data sets were generated or analysed during the current study.

Edoardo G. Giannini[1,2]
Mario Strazzabosco[2,3]

[1]*Gastroenterology Unit, Department of Internal Medicine, University of Genoa, Genoa, Italy*
[2]*Digestive Diseases Section, Department of Internal Medicine, Liver Center, Yale University School of Medicine, New Haven, Connecticut, USA*
[3]*Smilow Cancer Hospital and Liver Cancer Program, New Haven, Connecticut, USA*

Correspondence
Edoardo G. Giannini, Gastroenterology Unit, Department of Internal Medicine, University of Genoa, Viale Benedetto XV, no. 6, Genoa 16132, Italy.
Email: egiannini@unige.it

ORCID

Edoardo G. Giannini https://orcid.org/0000-0001-8526-837X
Mario Strazzabosco https://orcid.org/0000-0002-1995-6331

REFERENCES

1. Su T-H, Hsu S-J, Kao J-H. Paradigm shift in the treatment options of hepatocellular carcinoma. *Liver Int*. 2022;42:2067-2079.
2. Kudo M, Finn RS, Qin S, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. *Lancet*. 2018;391(10126):1163-1173.
3. Cheng AL, Qin S, Ikeda M, et al. Updated efficacy and safety data from IMbrave150: Atezolizumab plus bevacizumab vs. sorafenib for unresectable hepatocellular carcinoma. *J Hepatol*. 2022;76(4):862-873.
4. Vitale A, Finotti M, Trevisani F, Farinati F, Giannini EG. Treatment allocation in patients with hepatocellular carcinoma: need for a paradigm shift? *Liver Cancer Int*. 2022;3:34-36. doi:10.1002/lci2.42
5. Kudo M, Ueshima K, Chan S, et al. Lenvatinib as an initial treatment in patients with intermediate-stage hepatocellular carcinoma beyond up-to-seven criteria and child-Pugh a liver function: a proof-of-concept study. *Cancers (Basel)*. 2019;11(8):1084.
6. Kudo M. New treatment paradigm with systemic therapy in intermediate-stage hepatocellular carcinoma. *Int J Clin Oncol*. 2022;27(7):1110-1119.
7. Kudo M. A novel treatment strategy for patients with intermediate-stage HCC who are not suitable for TACE: upfront systemic therapy followed by curative conversion. *Liver Cancer*. 2021;10(6):539-544.
8. Tada T, Kumada T, Hiraoka A, et al. Comparison of prognostic impact of atezolizumab plus bevacizumab versus lenvatinib in patients with intermediate-stage hepatocellular carcinoma. *Liver Int*. 2023. doi:10.1111/liv.15753
9. Torres F, Ríos J, Saez-Peñataro J, Pontes C. Is propensity score analysis a valid surrogate of randomization for the avoidance of allocation bias? *Semin Liver Dis*. 2017;37(3):275-286.
10. Plaz Torres MC, Lai Q, Piscaglia F, et al. Treatment of hepatocellular carcinoma with immune checkpoint inhibitors and applicability of first-line Atezolizumab/bevacizumab in a real-life setting. *J Clin Med*. 2021;10(15):3201.
11. Stefanini B, Bucci L, Santi V, et al. Potential feasibility of atezolizumab-bevacizumab therapy in patients with hepatocellular carcinoma treated with tyrosine-kinase inhibitors. *Dig Liver Dis*. 2022;54(11):1563-1572.
12. Garuti F, Neri A, Avanzato F, et al. The changing scenario of hepatocellular carcinoma in Italy: an update. *Liver Int*. 2021;41(3):585-597.
13. Terashima T, Yamashita T, Toyama T, et al. Surrogacy of time to progression for overall survival in advanced hepatocellular carcinoma treated with systemic therapy: a systematic review and meta-analysis of randomized controlled trials. *Liver Cancer*. 2019;8(2):130-139.

14. Singal AG, Llovet JM, Yarchoan M, et al. Practice guidance on prevention, diagnosis, and treatment of hepatocellular carcinoma. *Hepatology*. 2023. doi:10.1097/HEP.0000000000000466
15. Pasta A, Calabrese F, Jaffe A, et al. Safety and efficacy of atezolizumab/bevacizumab in patients with hepatocellular carcinoma and impaired liver function: a systematic review and meta-analysis. *Liver Cancer*. 2023. doi:10.1159/000533991
16. Rimini M, Persano M, Tada T, et al. Survival outcomes from atezolizumab plus bevacizumab versus Lenvatinib in Child Pugh B unresectable hepatocellular carcinoma patients. *J Cancer Res Clin Oncol*. 2023;149(10):7565-7577.
17. Gyawali B, Eisenhauer E, Tregear M, Booth CM. Progression-free survival: it is time for a new name. *Lancet Oncol*. 2022;23(3):328-330.
18. Gyawali B, Hey SP, Kesselheim AS. Evaluating the evidence behind the surrogate measures included in the FDA's table of surrogate endpoints as supporting approval of cancer drugs. *EClinicalMedicine*. 2020;13(21):100332.
19. Jaffe A, Taddei TH, Giannini EG, Ilagan-Ying YC, Colombo M, Strazzabosco M. Holistic management of hepatocellular carcinoma: the hepatologist's comprehensive playbook. *Liver Int*. 2022;42(12):2607-2619.
20. Cabibbo G, Aghemo A, Lai Q, Masarone M, Montagnese S. Ponziani FR; Italian Association for the Study of the Liver (AISF). Optimizing systemic therapy for advanced hepatocellular carcinoma: the key role of liver function. *Dig Liver Dis*. 2022;54(4):452-460.