Donafenib in Chinese patients with advanced hepatocellular carcinoma (HCC): Really a new standard of care, or should we change paradigm for drug development in HCC?

Francesca Negri,[1] Camillo Porta[2]

[1]Medical Oncology Unit, University Hospital of Parma, Parma; [2]Department of Biomedical Sciences & Human Oncology, University of Bari 'Aldo Moro', and Division of Medical Oncology, Azienda Ospedaliero-Universitaria Consorziale Policlinico, Bari, Italy

Liver cancer is the sixth most common cancer worldwide,[1] with over half of the new cases and death occurring in China. Hepatocellular carcinoma (HCC) accounts for 75-85% of primary liver cancers. Most patients are diagnosed at an advanced stage with poor survival rates;[1] thus, the diagnosis and treatment of HCC is a main public health concern, especially in China.

Donafenib is a novel oral small-molecule inhibitor of multiple tyrosine kinases, such as vascular endothelial growth factor receptors, platelet-derived growth factor receptor, and Raf kinases, thereby blocking both angiogenesis and tumor cell proliferation.[2] Donafenib is a derivative of sorafenib with a trideuterated N-methyl group, that may improve molecular stability and enhance the pharmacokinetic features.[2] Preclinical, phase Ia and Ib trials have shown favorable efficacy and safety profile.[2,3]

Qin *et al.*[4] recently reported in the *Journal of Clinical Oncology* the results from an open-label, randomized phase II-III trial, in which donafenib was compared with sorafenib, as first-line therapy in Chinese patients with unresectable or metastatic HCC. The trial showed the superiority of donafenib over sorafenib in increasing overall survival (OS) and thus the authors propose donafenib as '*new frontline standard for Chinese patients with advanced HCC*'.

Is this statement correct? Probably yes… Is this true also for non-Asian patients? Probably no… But, more importantly, which are the most relevant considerations we can draw from this study (and all the other first-line trials available)?

Despite the significant OS advantage observed (median OS: 12.1 *vs* 10.3 months; HR: 0.831; 95% CI: 0.699 to 0.988; P=0.0245), patients enrolled in the donafenib trial clearly differed from those enrolled in other globally-conducted first-line pivotal trials.[5,6] Indeed, although no differences were observed between treatment arms in terms of BCLC C stage, Child-Pugh score, and percentage of patients presenting with high AFP level, >90% of the enrolled patients were HBV positive, a well-known negative prognostic factor; furthermore, patients were also younger, median age being 53 years in both study arms, while it was constantly over 60 years (often well above this figure) in the sorafenib SHARP trial,[5] the lenvatinib REFLECT trial,[6] and the atezolizumab plus bevacizumab IMbrave 150 trial,[7] this latter study having shown a significant OS advantage (again over sorafenib) in all main patients' subgroups, including HBV-positive and Asian patients.[7]

Once again, in our opinion, '*... the issue is not the right drug* [or combination]*, but the right patient*'.[8]

Having, for the first time, at least three different options for the medical treatment of HCC patients, our choice should rely on more thorough biological and etiopathogenic considerations.

Possibly, donafenib could be the treatment option of choice in HBV-infected patients, a population which is more and more uncommon in western country, where the growing incidence of nonalcoholic fatty liver disease, now a recognized inflammatory disease,[9] could theoretically benefit more from an immunotherapy-containing regimen; whether bevacizumab or lenvatinib is the best drug to combine with immunotherapy remains to be proven. Recent studies have indeed clearly demonstrated the immunomodulatory activity of lenvatinib,[10] suggesting potential synergism with immune checkpoint inhibitors. Furthermore, the combination of lenvatinib with the anti-PD-1 antibody pembrolizumab yielded impressive results not only in kidney cancer,[11] but also in HCC, with a 46% objective response rate (95% CI, 36.0% to 56.3%), a 9.3-month median progression-free survival, and a 22-month median OS of 22 months, per mRECIST, within a phase Ib study.[12]

In our opinion, these considerations and hypotheses should be taken into account when designing the new generation of trials in HCC.

Correspondence: Camillo Porta, Department of Biomedical Sciences and Human Oncology, University of Bari 'A. Moro' and Division of Medical Oncology, Azienda Ospedaliero-Universitaria Consorziale Policlinico di Bari, piazza Giulio Cesare 11, 70124 Bari, Italy.
Tel.: +39.080.5594167 - Fax: +39.080.5593477.
E-mail: camillo.porta@gmail.com

Key words: Donafenib; sorafenib; hepatocellular carcinoma; Chinese patients; patients' selection.

Received for publication: 21 September 2021.
Accepted for publication: 21 September 2021.

Oncology Reviews 2021; 15:564
doi:10.4081/oncol.2021.564

References

1. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin 2021;71:209-49.
2. Li X, QiuM, Wang S, et al. A phase I dose-escalation, pharma-

cokinetics and food-effect study of oral donafenib in patients with advanced solid tumours. Cancer Chemother Pharmacol 2020;85:593-604.
3. Bi F, Qiu M, Chai X, et al. A multicenter phase II study of donafenib in patients with advanced hepatocellular carcinoma. J Clin Oncol 2017;35(Suppl.):abstr e15682.
4. Qin S, Bi F, Gu S, et al. Donafenib versus sorafenib in first-line treatment of unresectable or metastatic hepatocellular carcinoma: a randomized, open-label, parallel-controlled phase II-III trial. J Clin Oncol 2021;39:3002-11.
5. Llovet JM, Ricci S, Mazzaferro V, et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 2008;359:378-90.
6. 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;391:1163-73.
7. Finn RS, Qin S, Ikeda M, et al. Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma. N Engl J Med 2020;382:1894-05.
8. Porta C, Broglia C, Negri F. Medical treatment of advanced hepatocellular carcinoma patients: the issue is not the right drug, but the right patient. Hepatology 2019;70:429-30.
9. Farrell GC, Haczeyni F, Chitturi S. Pathogenesis of NASH: how metabolic complications of overnutrition favour lipotoxicity and pro-inflammatory fatty liver disease. Adv Exp Med Biol 2018;1061:19-44.
10. Zhao Y, Zhang YN, Wang KT, Chen L. Lenvatinib for hepatocellular carcinoma: From preclinical mechanisms to anti-cancer therapy. Biochim Biophys Acta Rev Cancer 2020;1874:188391.
11. Motzer R, Alekseev B, Rha SY, et al. Lenvatinib plus pembrolizumab or everolimus for advanced renal cell carcinoma. N Engl J Med 2021;384:1289-00.
12. Finn RS, Ikeda M, Zhu AX, et al. Phase Ib study of lenvatinib plus pembrolizumab in patients with unresectable hepatocellular carcinoma. J Clin Oncol 2020;38:2960-70.