Editorial Commentary

Tivozanib in advanced inoperable hepatocellular carcinoma: considerations for patients with liver cirrhosis

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Comment on: Fountzilas C, Gupta M, Lee S, *et al.* A multicentre phase 1b/2 study of tivozanib in patients with advanced inoperable hepatocellular carcinoma. Br J Cancer 2020;122:963-70.

Submitted Apr 25, 2020. Accepted for publication May 26, 2020.
doi: 10.21037/atm-20-3526
View this article at: http://dx.doi.org/10.21037/atm-20-3526

Liver cancer is the fourth leading cause of cancer-related death worldwide, with hepatocellular carcinoma (HCC) accounting for the majority of primary liver cancers (1). Approximately only 30–40% of patients with HCC are diagnosed at a very early or early stage according to the Barcelona Clinic Liver Cancer staging system, when potentially curative treatments (surgical resection, liver transplantation, or local ablation therapy) are employed as first-line treatment options (2). For patients with intermediate-stage HCC, locoregional therapies, including transarterial chemoembolization (TACE), can be applied. Patients who have advanced HCC with major vessel invasion, lymph node involvement, and/or extrahepatic metastasis or patients who experience progressive HCC refractory to TACE may be candidates for systemic therapy if underlying liver function and performance status are well preserved (3,4). Unfortunately, more than half of patients with HCC are still diagnosed at an advanced stage globally (5). Thus, researchers and pharmaceutical companies have endeavored to understand HCC tumorigenesis, with tremendous developments and a change of paradigm in systemic therapies made following a number of trials. The use of sorafenib, as a systemic treatment initially led to significant improvement in overall survival (OS) among patients with advanced HCC (6). In the past few years, lenvatinib (7) has been approved as another first-line systemic treatment, while two programmed death-1 (PD-1) inhibitors [i.e., nivolumab (8), pembrolizumab (9), cabozantinib (10), and ramucirumab (11)] were approved as second-line treatment. However, the high incidence of underlying cirrhosis and the delayed diagnosis of HCC may interfere with the above treatments (3).

Meanwhile, tivozanib, an oral tyrosine kinase inhibitor (TKI), is a third-generation inhibitor of vascular endothelial growth factor receptor (VEGFR)-1, -2, and -3, showing high *in vitro* inhibitory activity against VEGFRs. Owing to favorable pharmacodynamic (PD) profiles in absorption, distribution, and elimination, tivozanib is expected to provide benefits in clinical practice (12). In a phase 3 trial, tivozanib therapy led to significantly superior progression-free survival (PFS), objective response rate (ORR), and safety profiles in patients with metastatic renal cell carcinoma (RCC) compared to sorafenib (13). As the inhibition of VEGFRs is reportedly beneficial in HCC (14), tivozanib can be a potential candidate drug for HCC. However, considering a majority of HCC patients have underlying liver cirrhosis (3), it would be necessary to re-estimate the optimal dose of tivozanib for such patients.

In a recent issue of *British Journal of Cancer*, Fountzilas and colleagues reported on the safety, dosing, pharmacokinetics (PK), PD, and anti-tumor activity of tivozanib in a total of 27 cirrhotic patients with advanced HCC whose liver function was well preserved as Child-Turcotte-Pugh (CTP) class A (15). In the present phase 1b/2 study, considering results from a preceding phase 1 study of tivozanib on patients with various advanced, refractory solid tumors (16) and the presence of cirrhosis in included patients, the starting dose (level 1) was reduced from 1.5 to 1.0 mg. The maximum-tolerated dose and recommended phase 2 dose was determined to be 1.0 mg,

once daily, for 21 days followed by 7 days off-treatment on a 28-day cycle through the phase 1b part of this trial due to its dose-limiting toxicity. Median PFS and OS were 24 weeks and 9 months, respectively, and the ORR was 21% according to Response Evaluation Criteria in Solid Tumors 1.1 (15). This is the first study to report the response of tivozanib in patients with advanced HCC and cirrhosis.

On this issue, even though tivozanib failed to meet the pre-defined threshold (true progression rate of less than P0=0.5) and the investigators decided not to proceed to stage 2 of a phase 2 trial, this study is an important reference for second movers in estimating the safety and efficacy of tivozanib in patients with HCC. A sequel phase 1/2 trial of tivozanib in combination with durvalumab, a PD-1 ligand (PD-L1) inhibitor (NCT03970616), is recruiting patients since the ORR in patients treated with tivozanib was favorable. The synergistic effects of immune checkpoint inhibitors (ICIs) and angiogenesis inhibitors in combination with VEGFR inhibitors are drawing increasing attention after a very recent interim analysis of the IMbrave150 study showed a positive impact of atezolizumab (a PD-L1 inhibitor) and bevacizumab (a VEGFR inhibitor) on OS, PFS, and ORR over sorafenib. As a result, expected practice in first-line treatment for HCC may change (17). In a similar case, axitinib, which failed to improve OS over placebo in a phase 2 trial, was used to complete a phase 1 trial combination with avelumab (another PD-L1 inhibitor), showing a prolonged PFS and time to tumor progression (18).

Another attainment from the present study relates to safety. A recent network meta-analysis analyzing the safety of TKIs for RCC showed that tivozanib had a more favorable safety profile with a lower risk of grade 3 or 4 adverse events than other TKIs such as sorafenib, sunitinib, and cabozantinib (19). The authors observed the low incidence of severe liver toxicity, hand-foot-skin reactions, hypertension, and the absence of deaths due to toxicity (15). However, it is notable that the present study was conducted in patients with cirrhosis. In previous studies, including in patients with RCC, only patients with "sufficient" hepatic functional reservoir and those without chronic hepatitis B or C infection were included. All VEGFR-TKIs are mainly metabolized in the liver, especially by CYP3A4, although tivozanib is relatively less affected by CYP3A4 than other VEGFR-TKIs (12). CYP3A4, isoenzymes and their activity are reduced in patients with cirrhosis (20). In individual tivozanib exposure data suggested by the authors (supplement table 5), the maximum concentration for each patient was observed over a wide range which may have been due to different residual hepatic reservoir. Besides CYP3A4, several factors exist that may influence the PK/PD profile, efficacy, and safety of TKIs in cirrhotic patients: portosystemic shunt, enterohepatic recirculation, biliary excretion, and drug reabsorption through gastrointestinal tract (21). In particular, in the case of patients with ascites (even in CTP class A6 cirrhosis), a portosystemic shunt with an increased hepatic venous pressure gradient resulted in the reduced first-pass metabolism of high-extraction ratio drugs and caused increased toxicity (22). In a previous study, patients with HCC underlying CTP class B cirrhosis under treatment with sorafenib showed significantly shorter survival and worse safety profiles compared to patients with CTP class A cirrhosis (23); moreover, a significant difference in OS existed even in the same CTP class A (5 *vs*. 6) (24).

In the present trial, the inclusion and exclusion criteria did not exclude unfavorable prognostic factors (i.e., ≥50% liver occupation, bile duct invasion, portal vein invasion, and lymph node involvement) that were excluded in the preceding phase 3 trials of TKIs in patients with HCC. Since the amount of immune suppressor cells (e.g., myeloid-derived suppressor cells, regulatory T cells, etc.) are positively associated with tumor volume, a larger tumor volume is known to be a predictor of a lower response rate and a worse prognosis (25). Thus, the clinical effect of tivozanib could be underestimated in the current study. As a sequel trial with tivozanib in combination with durvalumab (NCT03970616) had stricter selection criteria that excluded patients with tumor thrombus in the portal vein and inferior vena cava, the effect of tivozanib is expected to be better.

In summary, Fountzilas *et al*. suggested a dose of tivozanib for cirrhotic patients with HCC, which can be referred to by the next phase 2 study of tivozanib. Although the current study failed to proceed to stage 2 of a phase 2 trial, tivozanib showed a favorable response rate, PK/PD profiles, and safety profiles. We hopefully anticipate that tivozanib, in combination with durvalumab, will show a clinical benefit in a currently ongoing trial.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Annals of Translational Medicine*. The article did not undergo external peer review.

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/atm-20-3526). The authors have no conflicts of interests to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Oh H, Lee JH. Tivozanib in advanced inoperable hepatocellular carcinoma: considerations for patients with liver cirrhosis. Ann Transl Med 2020;8(22):1530. doi: 10.21037/atm-20-3526