Viewpoint

Weight-based dosing of lenvatinib for advanced hepatocellular carcinoma

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Lenvatinib is an oral molecular target agent that blocks vascular endothelial growth factor receptors 1–3, fibroblast growth factor receptors 1–4, platelet-derived growth factor receptor α, *RET*, and *KIT*. It is noninferior, but not statistically superior, to sorafenib with regard to overall survival, according to the findings of a phase 3 trial of lenvatinib versus sorafenib as first-line therapy for advanced hepatocellular carcinoma (HCC) (the REFLECT trial) (1). Nowadays, lenvatinib has been approved all over the world and has become the second front-line tyrosine kinase inhibitor in patients with advanced HCC. The recommendations for starting lenvatinib therapy for advanced HCC are different from those for other molecular target agents in patient with advanced HCC in that dose is based on body weight (≥60 kg: 12 mg once daily; <60 kg: 8 mg once daily). The aim of this article is to discuss the weight-based dosing of lenvatinib for advanced HCC.

Lenvatinib was developed for the treatment of radioiodine-refractory differentiated thyroid cancer before its use in treating advanced HCC was considered. The initial dose of lenvatinib for thyroid cancer was defined as 24 mg once daily (2). HCC occurs predominantly in patients with underlying chronic liver disease and cirrhosis. When lenvatinib was developed for use in patients with advanced HCC, the starting dose was reevaluated according to recommendations (3). In phase 1 of the REFLECT study, which focused on HCC, 20 patients (9 with Child-Pugh class A disease and 11 with Child-Pugh class B disease) were enrolled (4). The maximum tolerable dose for patients with Child-Pugh A and B class advanced HCC was reported to be 12 and 8 mg once daily, respectively. This recommended dosage was used in a single-arm, open-label, multicenter phase 2 study (5). In Japan and Korea, 46 patients with advanced HCC who did not qualify for surgical resection or local therapies were enrolled this study and received lenvatinib at a dosage of 12 mg once daily. The median time before the disease began to progress again was 7.4 months, and the objective response rate was 37%.

Because of adverse events, the dosage had to be modified for 74% of the patients, and 22% had to discontinue the drug. The patients who required dose modification or had to discontinue treatment within 30 days had a lower median body weight (54.1 kg) than did patients who did not required regimen change (67.9 kg). Moreover, in this study, pre-dosing blood samples were obtained for pharmacokinetic assessments on days 1, 8, 15, and 22 of cycle 1 and on day 1 of cycles 2 and 3. The median trough concentrations on day 15 of cycle 1 in patients who required dose modifications and in those who did not were 62.4 and 33.0 ng/mL, respectively.

Before a phase 3 study, an additional optimal dose assessment study for patients with Child-Pugh class A advanced HCC was conducted with pooled data from the phase 2 study (6). This population pharmacokinetic analysis confirmed the exposure–response relationship with regard to safety and efficacy in patients with advanced HCC who received lenvatinib, 12 mg once daily. The results of this study showed a strong exposure-response relationship, between high area under the curve (AUC) for lenvatinib and low body weight (best cutoff values for lenvatinib AUC and body weight were 2,430 ng/mL and 57.8 kg, respectively). This relationship could be used to predict which patients were likely to need dose modification or treatment discontinuation. According to these findings, the recommended starting doses for patients weighing 60 kg or more and those weighing less than 60 kg were 12 and 8 mg, respectively.

The REFLECT trial was the international, multicenter, randomized, open-label study conducted with 954 patients who had previously untreated, metastatic, or unresectable HCC. Patients were randomly assigned, in a 1:1 ratio, to receive either lenvatinib (12 mg orally once daily for patients with a baseline body weight of 60 kg or more and 8 mg orally once daily for patients with a baseline body weight of less than 60 kg) or sorafenib (400 mg orally twice daily, regardless of weight). Treatment continued either until disease progression was confirmed radiologically or if toxic effects were unacceptable. Subgroup analyses in the REFLECT trial indicated that the overall lengths of survival of patients receiving lenvatinib who weighed 60 kg or more and those who weighed less than 60 kg were 13.4 and 13.7 months, respectively; for patients weighing 60 kg or more, the hazard ratio (HR, in contrast to sorafenib) was 0.85 [95% confidence interval (CI), 0.65 to 1.11], and for those weighing less than 60 kg, HR=0.95 (95% CI, 0.79 to 1.14) (7). Moreover, in the two groups of patients with different weights, the mean dose intensities of lenvatinib and rates of occurrence of common adverse events (hypertension, diarrhea, decreased appetite, weight loss, and fatigue) were similar. These data confirmed that basing the starting dosage of lenvatinib on weight was reasonable for patients with advanced HCC.

In conclusion, these findings might strongly contribute to the success of a phase 3 trial. A weight-based dosing approach should be followed when lenvatinib is used for advanced HCC in patients with Child-Pugh class A disease in real-world practice.

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Footnote

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