# HCC IN FOCUS

Current Developments in the Management of Hepatocellular Carcinoma

Section Editor: Robert G. Gish, MD

## Treatment of Hepatocellular Carcinoma With Lenvatinib

Kwang-Hyub Han, MD
Professor, Department of Internal Medicine
Yonsei University College of Medicine
Director, Yonsei Liver Center, Severance Hospital
Seoul, South Korea

### G&H What is the mechanism of action of lenvatinib?

**K-HH** Lenvatinib (Lenvima, Eisai) is a tyrosine kinase inhibitor selectively targeting vascular endothelial growth factor receptor (VEGFR) 1 to 3, fibroblast growth factor receptor (FGFR) 1 to 4, platelet-derived growth factor receptor α, RET, and KIT. According to preclinical research, this orally administered drug works by inhibiting angiogenesis driven by VEGF and by FGF as well as angiogenesis dependent on KIT, in addition to blocking RET fusion/RET mutant tumorigenesis, and lymphangiogenesis associated with VEGFR3.

### G&H In which countries is lenvatinib currently approved for the treatment of hepatocellular carcinoma, and for which patients is it indicated?

**K-HH** In March 2018, Japan was the first country to approve lenvatinib for the treatment of unresectable hepatocellular carcinoma (HCC). In August 2018, the drug was approved in the United States and in South Korea for first-line treatment of unresectable HCC, and was also given marketing authorization by the European Commission for use as a first-line therapeutic option in adult patients who have advanced or unresectable HCC and who have not had any previous systemic treatment. In September 2018, the drug was also approved in China to treat unresectable HCC in patients without prior systemic treatment.

It should be noted that lenvatinib is the first breakthrough after several failures in the first-line setting for HCC. Several compounds failed in randomized, controlled, phase 3 trials, not only in the first-line setting (sunitinib, brivanib, linifanib, erlotinib, doxorubicin) but also in the second-line setting (brivanib, everolimus, ramucirumab, tivantinib, ADI-PEG20, S-1). There are several reasons for these failures, but one involves the imbalance between efficacy and toxicity. Lenvatinib's high response rate and acceptable toxicity profile may be responsible for its success.

### G&H What are the key study findings on lenvatinib monotherapy for unresectable HCC?

**K-HH** The key study was the REFLECT trial, which was a phase 3, randomized, multicenter, open-label trial that evaluated the use of lenvatinib compared to sorafenib (Nexavar, Bayer) for first-line treatment of unresectable HCC. In this study (n=954), lenvatinib met the primary endpoint of overall survival, showing that the drug was noninferior to sorafenib. Median overall survival was 13.6 months with lenvatinib compared with 12.3 months with sorafenib. For the secondary endpoints of progression-free survival, objective response rate, and time to progression, lenvatinib was found to be superior, and have clinically meaningful improvements, compared to sorafenib.

### G&H What are the effects of lenvatinib on quality of life?

**K-HH** Quality of life was evaluated in the REFLECT trial using the validated European Organisation for Research and Treatment of Cancer (EORTC) quality-of-life questionnaire (QLQ) C30 and its HCC-specific module EORTC QLQ-HCC18. According to these instruments, lenvatinib was associated with delayed deterioration of role function, general cancer pain, diarrhea, nutrition, and body image compared with sorafenib. In particular for diarrhea and nutrition, there was a delay of over a month for symptom worsening in patients taking lenvatinib vs those taking sorafenib.

For the secondary endpoints of progression-free survival, objective response rate, and time to progression, lenvatinib was found to be superior, and have clinically meaningful improvements, compared to sorafenib.

**G&H** What are the most common adverse events associated with lenvatinib, and how do they compare with those associated with sorafenib?

**K-HH** According to findings of the REFLECT trial, treatment-emergent adverse events (TEAEs) of all grades appeared to be comparable in patients taking lenvatinib vs those taking sorafenib. However, it should be noted that patients in the lenvatinib arm were exposed to the drug 2 months longer than patients in the sorafenib arm. As long as the patient was on the drug, TEAEs were recorded, which also contributed to longer observational periods in the lenvatinib arm. After correcting for the actual treatment duration, the incidence of adverse events of all grades, adverse events of grade 3 or higher, and serious adverse events were either comparable between the 2 arms or lower in the lenvatinib arm.

Hypertension was the most common adverse event associated with lenvatinib. In addition, the drug was associated with less frequent hand-foot skin reaction than sorafenib. More data need to be collected to understand the potential safety profile of lenvatinib via real-world experiences.

**G&H** What is the optimal dose of lenvatinib? Can the drug be dose-reduced and -escalated effectively?

**K-HH** In the REFLECT trial, the mean dose intensity of lenvatinib was 10.5 mg/day for patients at least 60 kg and 7.0 mg/day for patients less than 60 kg (87.7% and 87.5% of the planned starting doses, respectively). Thus, it is recommended that patients at least 60 kg start with a dose of 12 mg and that patients less than 60 kg start with a dose of 8 mg (although clinical considerations may be needed for individual patients). When efficacy was compared between the 2 groups, there was no significant difference in clinical outcomes.

It may be necessary to reduce or interrupt doses to manage adverse events effectively. There are limited data regarding the safety and effectiveness of dose re-escalation for lenvatinib.

**G&H** What follow-up care is needed for patients taking lenvatinib?

**K-HH** Blood pressure, urine analysis, serum calcium level, serum thyroid-stimulating hormone level, and cardiac function should be monitored regularly in these patients. If patients have hypertension, the most common adverse event associated with lenvatinib, they should be prescribed an antihypertension drug.

**G&H** Thus far, how do real-world experiences seem to compare with the clinical trial data for this drug?

**K-HH** From what I have heard, lenvatinib has already been used in approximately 4000 patients in Japan since its approval. It has been used as first-line treatment in approximately 40% of patients, second-line treatment in another approximately 40%, and third-line treatment in approximately 15%, but good efficacy has been seen in all lines.

**G&H** What is the place of lenvatinib in the current treatment algorithm for HCC? Should this drug be used as first-line treatment instead of sorafenib, or vice versa?

**K-HH** According to the European Association for the Study of the Liver and the American Association for the Study of Liver Diseases, lenvatinib is a first-line treatment option equivalent to sorafenib. However, lenvatinib has shown a higher objective response rate and longer progression-free survival and time to progression compared to sorafenib. Moreover, patients treated with

sorafenib experienced more rapid decline in specific measures of quality of life compared to patients treated with lenvatinib, which means that the efficacy benefits seen with lenvatinib were not at the cost of quality of life compared to sorafenib. Therefore, the selection of lenvatinib as first-line therapy for unresectable HCC makes sense.

Which treatment should be chosen as the first line is an important matter in all cancers, including HCC. The first treatment can determine the future direction of therapy. If the response is good with the first treatment, a good response may also be seen with the next treatment. Conversely, if the response is poor with the first treatment, it is difficult to expect a good response with the second treatment. In addition, in unresectable HCC, 3 to 4 out of 10 patients may not be able to receive second-line therapy due to sudden liver failure. Considering all of these factors, I think that it is a good idea to use the most effective treatment as first-line therapy.

### G&H Which second-line drug should be used in patients who do not respond to lenvatinib?

**K-HH** Thus far, in South Korea, regorafenib (Stivarga, Bayer) and nivolumab (Opdivo, Bristol-Myers Squibb) are options for second-line therapy after the failure of sorafenib. However, there is no established line of therapy for patients after the failure of lenvatinib. Based on the fact that approximately 25% of patients who received lenvatinib as first-line therapy also received sorafenib in the REFLECT study, we can use sorafenib in real-world clinical settings after the failure of lenvatinib. In the REFLECT study, one-third of the overall patient population (156/478 patients randomized to lenvatinib and 184/476 to sorafenib) received subsequent anti-cancer medication, most commonly sorafenib (25% in the lenvatinib arm). Eastern Cooperative Oncology Group performance status and laboratory assessments, including liver function tests, were comparable between the arms prior to subsequent treatments. Among these patients, median overall survival was 21 vs 17 months, and the objective response rate was 27.6% vs 8.7% for the lenvatinib vs sorafenib arms, respectively.

### G&H What are the next steps in research involving the use of lenvatinib in HCC patients?

**K-HH** Perhaps lenvatinib should be studied in combination with chemoembolization in earlier-stage disease. Chemoembolization plus sorafenib has not been successful, but lenvatinib has a significantly higher response rate than sorafenib, so lenvatinib may have the potential to downstage the disease and allow for the subsequent use of local therapies.

In addition, we are currently awaiting results from a number of interesting ongoing studies with lenvatinib, such as in combination with nivolumab or pembrolizumab (Keytruda, Merck; ClinicalTrials.gov identifiers: NCT03418922 and NCT03006926, respectively), as well as a cost-effectiveness analysis from the REFLECT study.

*Dr Han is an advisory committee member of Eisai Co.*

## Suggested Reading


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