



REVIEW ARTICLE

Expert consensus on the management of adverse events in patients receiving lenvatinib for hepatocellular carcinoma

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Abstract

Lenvatinib is an oral multikinase inhibitor approved for use as first-line treatment for patients with advanced hepatocellular carcinoma (HCC). However, like other agents in this drug class, lenvatinib is associated with clinically important adverse events (AEs) that could adversely affect patient outcomes. Hypertension, diarrhea, decreased appetite/weight, hand–foot skin reaction, and proteinuria are among the most common AEs associated with lenvatinib therapy. This article provides strategies for the effective management of lenvatinib-associated AEs based on the expert opinion of authors and currently available literature. Due to the high risk of AEs in patients receiving lenvatinib, prophylactic measures and regular monitoring for AEs are recommended. Lenvatinib dose interruption, adjustment, or discontinuation of treatment may be required for patients who develop AEs. For grade 1 or 2 AEs, dose interruption is generally not required. For persistent or intolerable grade 2 or 3 AEs, lenvatinib treatment should be interrupted until symptoms improve/resolve to grade 0–1 or baseline levels. Thereafter, treatment should be resumed at the same or a lower dose. Disease progression may occur in patients who do not initially respond to treatment or receive a suboptimal lenvatinib dose following dose reduction, resulting in lack of efficacy. Therefore, to derive maximum treatment benefit and ensure long-term disease control, lenvatinib should be maintained at the highest possible dose when managing AEs. To conclude, lenvatinib-associated AEs can be managed with prophylactic measures, regular monitoring and symptomatic management, which can ensure continued treatment and maximum survival benefit in patients with advanced HCC receiving first-line lenvatinib therapy.

Introduction

Hepatocellular carcinoma (HCC) accounts for 90% of primary liver cancers and is the second leading cause of cancer deaths worldwide.¹ Advanced HCC has a poor prognosis, with an estimated median survival time of 6–8 months.¹ Sorafenib, a multikinase inhibitor, is the standard-of-care for patients with advanced HCC.^{1–3} Until recently, it was the only first-line systemic treatment available for patients with advanced disease. In 2018, another multikinase inhibitor, lenvatinib, was approved for the first-line treatment of patients with unresectable HCC.^{4,5}

Lenvatinib inhibits the kinase activities of vascular endothelial growth factor (VEGF) receptors VEGFR1, VEGFR2, and VEGFR3, as well as other proangiogenic and oncogenic pathway-related kinases, including fibroblast growth factor receptors 1, 2, 3, and 4; platelet-derived growth factor receptor alpha; KIT; and RET.^{4,5} An early phase 1/2 study in patients with advanced HCC demonstrated the clinical activity and acceptable

safety of lenvatinib.^{6,7} Pharmacokinetic and exposure-response analyses based on pooled data from this study and studies in healthy adults and patients with mixed tumor types determined the optimal starting dose for lenvatinib. In patients with HCC Child–Pugh class A, the recommended initial dose of lenvatinib is 12 mg once daily in patients with body weight \geq 60 kg and 8 mg once daily in those with body weight $<$ 60 kg.^{4,5,8}

The clinical efficacy of lenvatinib was confirmed in the Phase 3, open-label, multicenter, noninferiority REFLECT study (NCT01761266), which compared the efficacy and safety of lenvatinib *versus* that of sorafenib as first-line treatment for advanced unresectable HCC.⁹ Patients who had not received systemic treatment for advanced unresectable HCC were randomized to receive oral lenvatinib (12 mg once daily for body weight \geq 60 kg or 8 mg once daily for body weight $<$ 60 kg; $n = 478$) or sorafenib 400 mg twice-daily ($n = 476$) in 4-week cycles. Median overall survival (OS; primary endpoint) in the lenvatinib group was noninferior to that in the sorafenib group

(13.6 vs 12.3 months; hazard ratio [HR] 0.92; 95% confidence interval [CI] 0.79–1.06), as the upper limit of the two-sided 95% CI for HR was less than the predefined margin of 1.08. The median duration of follow-up at the time of primary analysis was 27.7 months in the lenvatinib group and 27.2 months in the sorafenib group. Secondary endpoints were also significantly (all $P < 0.0001$) improved with lenvatinib compared with sorafenib, including median progression-free survival (7.4 vs 3.7 months), median time to progression (8.9 vs 3.7 months) and objective response rate (24.1% vs 9.2%).⁹

Other than sorafenib, lenvatinib is the only first-line multikinase inhibitor that has demonstrated an OS benefit in patients with HCC.¹ However, like other multikinase inhibitors, lenvatinib is associated with clinically important adverse events (AEs) that could adversely affect patient outcomes.⁹ This article provides up-to-date strategies for the prompt and effective management of lenvatinib-associated AEs in patients with advanced HCC based on the expert opinion of authors and currently available literature.

Methods and search strategy

Consensus generation. Specialists in the management of HCC, who have experience of treating HCC patients with lenvatinib in Korea, provided their opinions on the management of lenvatinib-associated AEs. Consensus was derived after several rounds of discussion, including an online virtual meeting that was held in February 2021.

Literature review. PubMed was searched on January 5, 2021 using the search terms: lenvatinib, HCC, and management to identify articles supporting the use of lenvatinib for the treatment of HCC. Articles reporting the safety and tolerability of lenvatinib and strategies for the management of lenvatinib-associated AEs were selected for the review.

Tolerability and safety profile of lenvatinib in hepatocellular carcinoma

In the pivotal REFLECT study, treatment-emergent adverse events (TEAEs) occurred in 99% of patients in the lenvatinib group (18.9 episodes per patient-year), with 94% of patients experiencing treatment-related AEs.⁹ TEAEs of grade ≥ 3 severity were reported in 75% of lenvatinib recipients (3.2 episodes per patient-year), most of which were considered treatment-related (57% of patients).⁹

Hypertension was the most common TEAE in the lenvatinib group (42%), with the majority of events of grade ≥ 3 severity (23%).⁹ Other commonly (incidence $> 30\%$) occurring TEAEs with lenvatinib were diarrhea (39%), decreased appetite (34%) and decreased weight (31%); the most commonly (incidence $> 5\%$) reported grade ≥ 3 AEs with lenvatinib were increased blood bilirubin (7%) and proteinuria (6%).⁹

Serious treatment-emergent or treatment-related AEs occurred in 43% and 18% of patients in the lenvatinib group.⁹ The most common serious AE in the lenvatinib group was hepatic encephalopathy (4.4%).¹⁰ Treatment-related fatal AEs occurred in 11 (2%) patients receiving lenvatinib (including hepatic failure [$n = 3$],

cerebral hemorrhage [$n = 3$], and respiratory failure [$n = 2$]).⁹ Treatment-related AEs led to dose interruption in 40% of lenvatinib recipients, dose reduction in 37% of patients, and treatment withdrawal in 9% of patients.⁹

The tolerability and safety profile of lenvatinib in real-world studies^{11–20} was generally similar to that seen in the REFLECT trial.

Interestingly, a post-hoc analysis of the REFLECT study found that in patients treated with lenvatinib, some AEs were associated with longer OS.²¹ Median OS was significantly longer in patients with than in those without hypertension (18.0 vs 11.5 months; HR 0.64; 95% CI 0.52–0.80; $P < 0.001$), diarrhea (17.7 vs 11.6 months; HR 0.72; 95% CI 0.58–0.90; $P = 0.003$), proteinuria (18.6 vs 12.3 months; HR 0.76; 95% CI 0.60–0.98; $P = 0.03$), or hypothyroidism (19.8 vs 13.4 months; HR 0.72; 95% CI 0.54–0.96; $P = 0.024$).²¹ A retrospective, real-world study also found a significant association between longer OS and occurrence of hypertension ($P = 0.01$) or hand–foot syndrome ($P = 0.04$); on the other hand, appetite loss was significantly ($P = 0.01$) correlated with shorter OS.¹³ This study also showed that the median survival time was significantly ($P < 0.001$) longer in patients who did not require discontinuation of lenvatinib treatment due to serious AEs compared with those who did require discontinuation of treatment.¹³ In a recent real-world study in Korea, anorexia was the only factor associated with poor OS (HR 2.15; 95% CI 1.01–4.58) after adjustment for factors related to tumor burden and hepatic reserve function.¹⁹ Moreover, diarrhea and HFSR were shown to have the potential to predict longer PFS during lenvatinib therapy. Diarrhea was the only favorable prognostic factor for disease progression in multivariable analysis (HR 0.37; 95% CI 0.17–0.84, $P = 0.02$), while HFSR was only marginally associated (HR 0.51; 95% CI 0.24–1.08, $P = 0.08$).¹⁹ These results suggest that AEs may predict benefit with lenvatinib and careful management of AEs to avoid related treatment discontinuations may improve survival. However, further studies are required to confirm the correlation between AEs and clinical outcomes and to assess the role of baseline patient characteristics.

Dosage and administration of lenvatinib

It is recommended that health care professionals experienced in the use of anticancer therapies initiate lenvatinib therapy. The recommended starting dose of lenvatinib for patients with HCC is 8 mg once daily for those with a body weight of < 60 kg and 12 mg once daily for patients with a body weight of ≥ 60 kg. Lenvatinib is to be taken orally regardless of food. Dose interruption, adjustment, or discontinuation may be required to manage AEs associated with lenvatinib treatment. For mild to moderate adverse events, dose interruptions are generally not required unless AEs are intolerable despite optimal management. Recommended lenvatinib dose modifications are summarized in Table 1 and Common Terminology Criteria for Adverse Events (Version 5.0) definitions of grades 1–5 AEs are presented in Table S1.

Management of lenvatinib-associated adverse events

Based on available data from clinical studies, the majority of AEs in lenvatinib-treated patients with HCC occur in the first 1 to

Table 1 General recommendations for lenvatinib dose modifications in hepatocellular carcinoma patients^{4,5}

Body weight	Starting dose	Adverse reaction	Persistent and intolerable grade 2 or 3 toxicities [†]	Grade 4	
			Dose modification	Adjusted dose [‡]	
≥ 60 kg	12 mg od	1st occurrence [§]	Interrupt until resolved to Grade 0 or 1, or baseline ^{††}	8 mg od	Discontinue [¶]
		2nd occurrence		4 mg od	
		3rd occurrence		4 mg qod	
< 60 kg	8 mg od	1st occurrence [§]		4 mg od	
		2nd occurrence		4 mg qod	
		3rd occurrence		Discontinue	

od, once daily; qod, every other day.

[†]Medical management for nausea, vomiting, or diarrhea should be initiated prior to dose interruption or reduction.

[‡]Lenvatinib dose is to be reduced in succession based on the previous dose level (12, 8, 4, or 4 mg every other day).

[§]No dose adjustment required for first occurrence of hematological toxicity or proteinuria.

[¶]For hematologic toxicity, dosing can restart when resolved to grade 2 and, for proteinuria, dosing can resume when resolved to less than 2 g/24 h.

^{††}Excluding laboratory abnormalities judged to be non-life-threatening, which should be managed as grade 3.

2 months after starting treatment (Fig. 1).^{9,10} In addition to providing recommendations regarding the management of specific AEs in the following sections, Table 2 provides a summary of important monitoring tests that should be conducted before and during lenvatinib therapy.

Hypertension. Hypertension is the most frequently reported AE with lenvatinib therapy, usually occurring early in the course of treatment. In the REFLECT study, hypertension occurred in 42% of patients receiving lenvatinib, with the majority of events of grade ≥ 3 severity (23%).⁹ The median time to first onset was

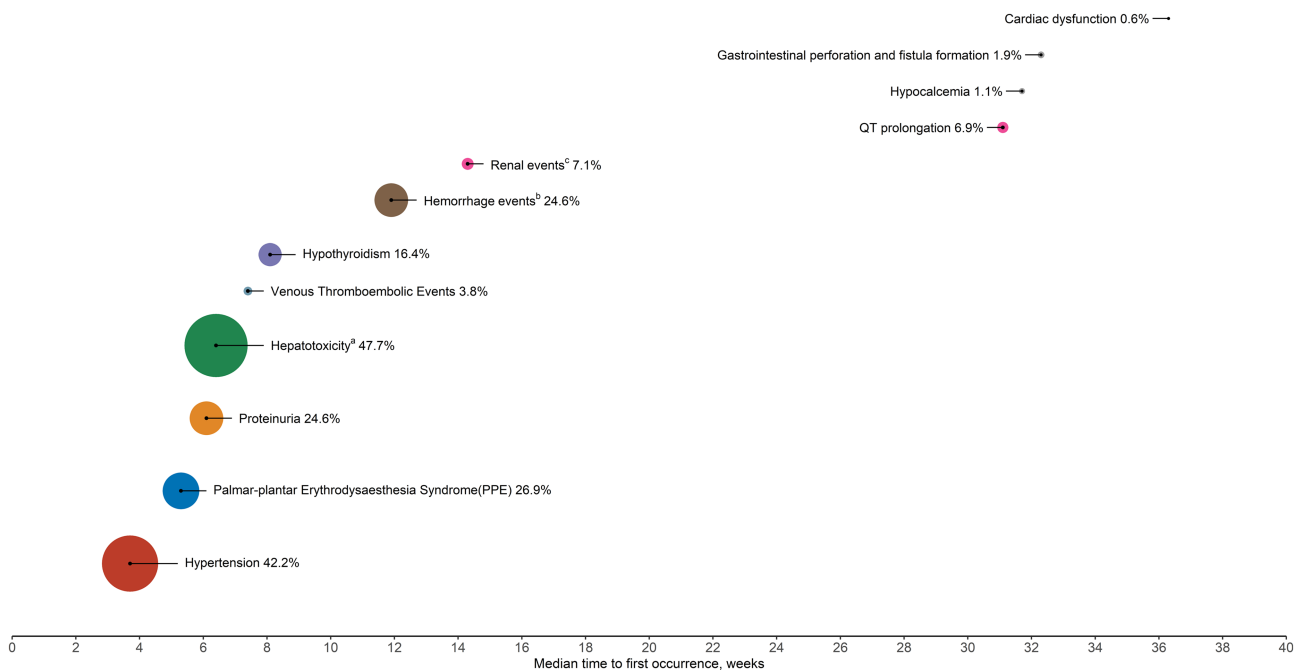


Figure 1 Incidence (%) and median time to onset of selected adverse events in patients with hepatocellular carcinoma treated with lenvatinib. Based on available data from clinical trials,^{9,10} the size of the circle is proportional to the incidence. ^aHepatotoxicity includes blood bilirubin increase, ascites, AST/ALT increased, hypoalbuminemia, hepatic encephalopathy, gamma-glutamyltransferase increase, hepatic failure, hepatic function abnormal, hyperbilirubinemia, hyperammonemia, jaundice cholestatic, hepatic pain, jaundice, urine bilirubin increased, hepatic cirrhosis, coma hepatic, edema due to hepatic disease, varices esophageal, and portal hypertensive gastropathy. ^bMost frequently reported hemorrhage events were epistaxis, hematuria, and gingival bleeding. Grade ≥ 3 events occurred in 24 subjects (5.0%) in the lenvatinib arm. ^cThe most frequently reported renal events were blood creatinine increased, acute kidney injury, and renal impairment. Grade ≥ 3 events occurred in 9 subjects (1.9%) in the lenvatinib arm.

Table 2 Adverse event monitoring before and during lenvatinib treatment

Test	Baseline		Treatment								
	0	1	2	3	4	5	6	7	8	Regular follow-up visits	
Liver function test (e.g., AST, ALT, ALP, bilirubin, and GGT)	•		•		•					•	•
Thyroid function test (TSH)	•				•					•	•
Hematology and clinical chemistry	•				•					•	•
Urinalysis	•			•	•					•	•
12-Lead ECG	•										
Blood pressure [†]	•		•	•	•		•			•	•
Vital signs and weight (e.g., fatigue and appetite)	•			•	•					•	•

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ECG, electrocardiogram; GGT, gamma-glutamyltransferase.

[†]Blood pressure should be monitored after 1 week, then every 2 weeks for the first 2 months, and at least monthly thereafter during treatment.

3.7 weeks.¹⁰ Hypertension events led to dose interruption in 3.6% of lenvatinib recipients and dose reduction in 3.4% of patients; one (0.2%) patient discontinued lenvatinib due to hypertension.¹⁰ Subgroup analyses suggested that the incidence of grade ≥ 3 hypertension events was higher in patients aged ≥ 75 years and in female patients.¹⁰

Given the early onset and high rate of hypertension, and to avoid complications associated with excessive/prolonged elevation of blood pressure (BP), it is crucial that hypertension be managed aggressively. Prior to initiating lenvatinib therapy, it is recommended that a formal risk assessment for potential cardiovascular complications be conducted.²² Patients known to be hypertensive should be on a stable dose of antihypertensive therapy for at least 1 week prior to lenvatinib treatment.^{4,5} The Cardiovascular Toxicities Panel recommended a BP treatment goal of $< 140/90$ mmHg in most patients receiving VEGF inhibitor therapy, and a lower BP target in patients with specific pre-existing cardiovascular risk factors (e.g. diabetes and/or chronic kidney disease).²² The panel recommended that BP be actively monitored throughout treatment with VEGF inhibitors, with more frequent assessments during the first treatment cycle.²² Based on this guidance, it is recommended that in patients receiving lenvatinib, BP should be monitored after 1 week of treatment, then every 2 weeks for the first 2 months, and monthly thereafter either at the clinic or at home.^{4,5}

For patients with systolic BP (SBP) ≥ 140 mmHg to < 160 mmHg or diastolic BP (DBP) ≥ 90 mmHg to < 100 mmHg (grade 2 hypertension), lenvatinib treatment should be continued (Fig. 2). Antihypertensive therapy should be initiated in these patients (if not already receiving it), or the dose of current antihypertensive therapy should be increased or an additional antihypertensive therapy added.^{4,5,23} In patients presenting with SBP ≥ 160 mmHg or diastolic BP ≥ 100 mmHg (grade 3 hypertension) despite optimal antihypertensive therapy, treatment with lenvatinib should be withheld and subsequently resumed at a lower dose when SBP is ≤ 150 mmHg and DBP is ≤ 95 mmHg, and the patient has been on a stable dose of antihypertensive therapy for at least 48 h (refer to Table 1 for dosage adjustment).^{4,5,23}

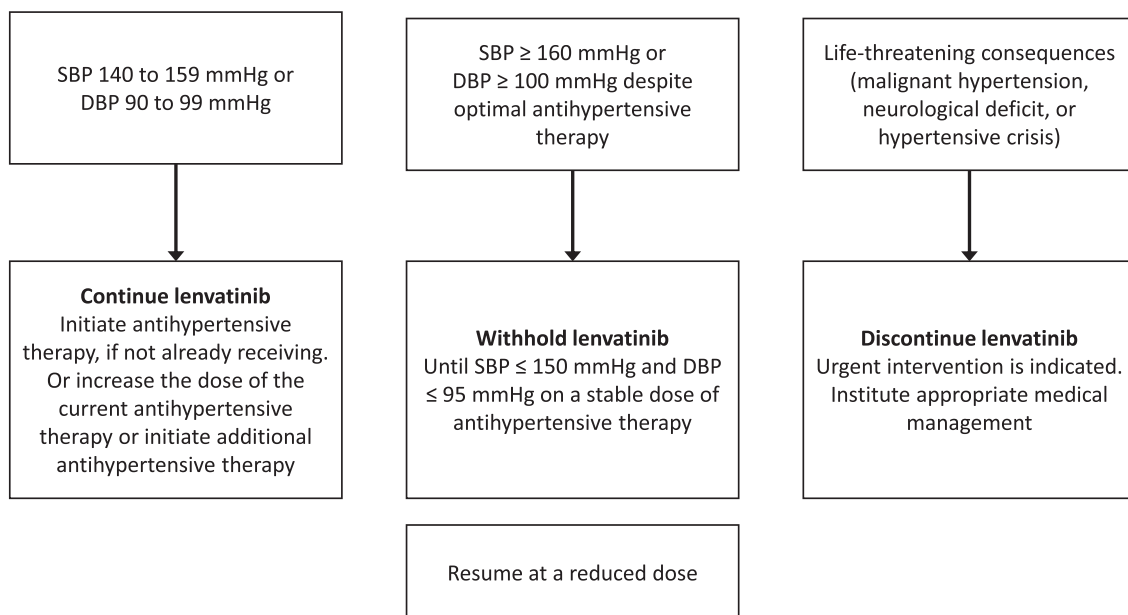


Figure 2 Management of hypertension.

In the event of life-threatening consequences of hypertension (grade 4 hypertension; e.g. malignant hypertension, neurological deficit, or hypertensive crisis), urgent intervention is required; treatment with lenvatinib should be discontinued and appropriate medical management instituted.^{4,5}

There is no robust evidence for the choice of antihypertensive agents in patients who are receiving lenvatinib.^{24–27} Angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), calcium channel blockers (CCBs), and beta blockers can be used.²⁷ However, diuretics are not recommended as first-line agents as they may worsen dehydration and electrolyte imbalance when diarrhea, a frequent adverse effect of lenvatinib, occurs.²⁶ An ACEI or ARB may be preferred if proteinuria is present^{24,25}; however, clear recommendations cannot be made, in view of earlier conflicting reports.^{28,29} Non-dihydropyridine CCBs such as verapamil and diltiazem are generally not recommended for patients receiving chemotherapy because they are cytochrome P450 (CYP) 3A4 inhibitors and may lead to drug–drug interactions.^{24,27} However, they do not necessarily have to be avoided in patients receiving lenvatinib because CYP3A4 inducers or inhibitors have a minimal effect on lenvatinib exposure.^{4,5} Nifedipine, a dihydropyridine CCB, should also be avoided, because of a possible effect on inducing VEGF secretion.³⁰

Expert recommendations.

- Hypertension must be managed aggressively.
- BP should be monitored after 1 week of lenvatinib treatment, then every 2 weeks for the first 2 months, and monthly thereafter either at the clinic or at home.
- Although there is no robust evidence for choice of antihypertensive, ACEIs, ARBs, CCBs, and beta blockers can be used depending on the patient's clinical circumstances and standard medical practice.
- Lenvatinib dose interruption, reduction, or discontinuation may be necessary if treated hypertension remains uncontrolled.

Proteinuria. Proteinuria has been reported in patients receiving lenvatinib treatment, which occurs early in the course of treatment (Fig. 1). Proteinuria is a common AE associated with VEGF inhibitors, and the postulated pathogenesis involves VEGF inhibition-derived changes in glomerular architecture and impairments in filtration function resulting from reduced nephrin production.³¹ Hypertension is a risk factor for the development of proteinuria; moreover, proteinuria is associated with increased risk of mortality, myocardial infarction, and progression to kidney failure.^{32,33}

In the pivotal REFLECT study, proteinuria occurred in 25% of lenvatinib recipients, with AEs of grade 3 severity reported in 6% of patients in the lenvatinib group.⁹ The median time to first onset was 6.1 weeks in patients receiving lenvatinib.¹⁰ Serious AEs of proteinuria occurred in 0.6% of lenvatinib recipients. Proteinuria events led to dose interruption in 6.9% and dose reduction in 2.5% of lenvatinib recipients, and three patients (0.6%) discontinued lenvatinib treatment due to proteinuria.¹⁰ The incidence of

grade ≥ 3 AEs appeared to be higher in Asian patients compared with Caucasians and in patients aged ≥ 65 years compared with patients aged < 65 years.¹⁰

Patients should be assessed for proteinuria prior to initiating treatment and monitored regularly.²³ Based on our clinical experience, patients are generally monitored every 2 weeks during the first month, then monthly thereafter, with regular follow-up visits. Lenvatinib dose interruptions, adjustments (Table 1), or discontinuation of treatment, may be required if proteinuria of $\geq 2+$ is detected (Fig. 3).^{4,5} Proteinuria can be assessed by dipstick test, random urine collection, 24-h urine collection, and/or urine protein-to-creatinine ratio (UPCR), depending on the judgment of clinicians. However, because 24-h urine collection is inconvenient for patients, and can be misleading if urine collection is incomplete,³⁴ UPCR is the preferred method in our experience. In real-world clinical practice, if urine dipstick proteinuria is $\geq 2+$, random UPCR can be checked. A UPCR cut-off value of 2.4 shows a high level of correlation with Grade 3 proteinuria measured by 24-h urine collection (≥ 3.5 g/24 h).³⁵ Therefore, if UPCR is ≥ 2.4 , a 24-h urine collection can be considered to determine the grade of proteinuria. In patients with proteinuria of ≥ 2 g/24 h,^{4,5} or if proteinuria of < 2 g/24 h is accompanied by edema, plural effusion, ascites, or increased serum creatinine, lenvatinib dose interruption is recommended.²³ Once proteinuria resolves to < 2 g/24 h, treatment can be resumed at the same dose (first occurrence) or after dose reduction (second occurrence; Table 1).^{4,5} In the event of nephrotic syndrome (> 3.5 g/24 h), treatment with lenvatinib should be discontinued and not resumed.^{4,5}

Expert recommendations. Based on our clinical experience, patients are generally monitored every 2 weeks during the first month, then monthly thereafter, with regular follow-up visits. Lenvatinib dose interruptions, adjustments, or discontinuation of treatment may be required if proteinuria of $\geq 2+$ is detected.

Diarrhea. Diarrhea occurs frequently and usually early during treatment with lenvatinib. In the REFLECT study, diarrhea occurred in 39% of lenvatinib recipients, with most events of mild or moderate severity (Grade ≥ 3 events occurred in 4% of patients).⁹ Medical management for diarrhea should be instituted promptly to prevent dehydration, electrolyte imbalance, poor quality of life, and intolerance to cancer treatment and started prior to lenvatinib dose interruption or reduction (Table 1).^{4,5} The treatment approach for diarrhea generally includes dietary adjustments such as avoiding caffeine, dairy, and greasy foods (which can worsen gastrointestinal distress); symptomatic control of diarrhea; and monitoring/managing electrolytes. For patients who are taking lactulose, the dose may be decreased. Patients receiving a diuretic for the treatment of hypertension should be monitored for the development of dehydration associated with diarrhea.²³ Supportive therapy with an antidiarrheal agent, such as loperamide, should be considered on an as-needed basis.³⁶ mg (two tablets) initially, followed by 2 mg (one tablet) after every loose stool, not earlier than 2–3 h after the initial dose. The maximum daily dose should not exceed 12 mg (six tablets) in adults and 8 mg (four tablets) in adolescents.³⁷ Other useful treatments for diarrhea include dioctahedral smectite,³⁸ budesonide, and the combination of

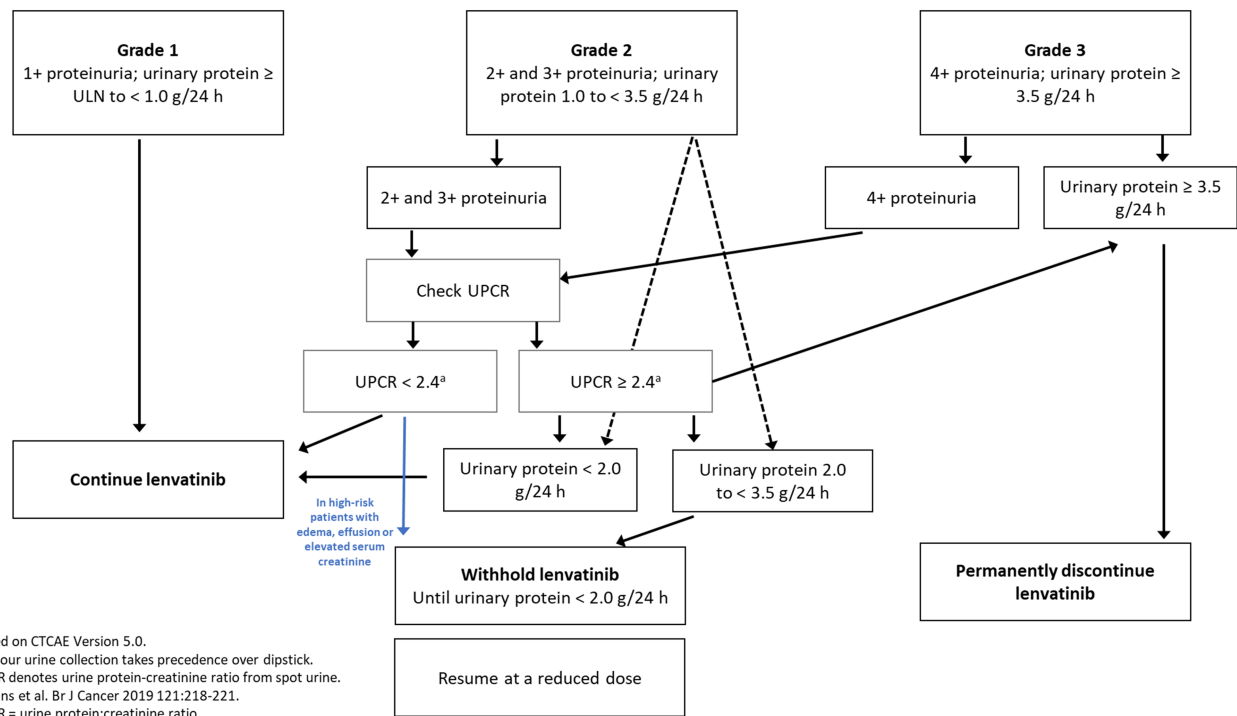


Figure 3 Management of proteinuria to enable continuation of lenvatinib treatment.

diphenoxylate and atropine.³⁶ Lenvatinib dose interruption and subsequent dose reduction is required for patients with persistent or intolerable grade 2 or 3 diarrhea, and lenvatinib treatment should be discontinued if grade 4 diarrhea persists despite medical management.^{4,5,36}

Expert recommendations.

- Medical management for diarrhea should be instituted promptly to prevent dehydration, electrolyte imbalance, poor quality of life, and intolerance to cancer treatment and started prior to lenvatinib dose interruption or reduction.

Palmar plantar erythrodysesthesia syndrome/hand-foot skin reaction.

Palmar plantar erythrodysesthesia syndrome/hand-foot skin reaction (HFSR) is a cutaneous adverse event characterized by redness, marked discomfort, swelling, and tingling in the palms of the hands or the soles of the feet.³⁹ In the REFLECT study, HFSR occurred in 27% of lenvatinib recipients, with grade ≥ 3 AEs reported in 3% of patients.⁹ The median time to first onset was 5.3 weeks in patients receiving lenvatinib.¹⁰ No serious AEs of HFSR or discontinuations because of HFSR were reported in lenvatinib recipients.¹⁰ The incidence of grade ≥ 3 HFSR appeared to be higher in Asian compared with White subjects and the incidence of HFSR appeared to be lower in patients aged ≥ 75 years.¹⁰

Based on recommendations for managing HFSR caused by multikinase inhibitors,⁴⁰⁻⁴² patients receiving lenvatinib should be advised to take prophylactic measures before HFSR symptoms

develop, such as emollients and urea-containing prescription agents, and regularly monitored during lenvatinib treatment (Table 3). If grade 1 HFSR develops, lenvatinib treatment can be continued, as long as there is no pain (Table 3). If pain occurs (grade 2 symptoms), treatment with lenvatinib treatment should be interrupted and patients treated with steroids. After pain is alleviated, lenvatinib treatment should be resumed at the same dose if pain had occurred after several weeks of pain-free treatment and at a reduced dose if dose interruption was required within 1 week of initiating treatment (Table 1).

Expert recommendations.

- Patients should be advised to take prophylactic measures before HFSR symptoms develop, such as emollients and urea-containing prescription agents, and regularly monitored during lenvatinib treatment.
- Lenvatinib interruption or dose reduction may be necessary if grade 2 or 3 symptoms are present.

Decreased appetite and weight loss.

Decreased appetite and weight loss are also common occurrences in patients receiving lenvatinib. In the REFLECT study, 34% of lenvatinib recipients reported a decrease in appetite (grade ≥ 3 AEs in 5% of patients), and 31% of patients reported a decrease in body weight (grade ≥ 3 AEs 8% of patients).⁹ Decreased body weight led to dose interruption or reduction in 4.2% of lenvatinib recipients.¹⁰

Table 3 Recommendations for the management of HFSR

HFSR severity	Intervention
No HFSR	Maintain frequent contact with physician to ensure early diagnosis of HFSR
Therapy initiation	Full-body skin examination, pedicure; wear thick cotton gloves and/or socks; avoid hot water, constrictive footwear, and excessive friction
Grade 1	If symptoms develop at 2-week clinical evaluation or within first month, proceed to next step ... Maintain current dose of lenvatinib; monitor patient for change in severity
<ul style="list-style-type: none"> • Numbness • Tingling • Dysesthesia • Paresthesia • Painless swelling • Erythema • Discomfort of hands or feet • No interference with ADL 	Avoid hot water; use moisturizing creams for relief; wear thick cotton gloves and/or socks; use a 20–40% urea-based cream to aid exfoliation
Grade 2	If symptoms worsen after clinical evaluation at 2 weeks, proceed to next step ... Dose reduction to 50% of dose for 7–28 days
<ul style="list-style-type: none"> • Painful erythema • Swelling of hands and/or feet • Interference with patients ADL 	Treat as with grade 1 toxicity, with the following additions: topical steroid ointment, codeine, pregabalin for pain; follow dose modifications listed in Table 1
Grade 3	If symptoms worsen after clinical evaluation at 2 weeks, proceed to next step ... Interrupt treatment for 7 days and until improvement to grade 0–1
<ul style="list-style-type: none"> • Moist desquamation • Ulceration • Blistering • Severe pain of hands and/or feet • Patient unable to perform ADL 	Treat as with Grades 1 and 2; follow dose modifications listed in Table 1

ADL, activities of daily living; HFSR, hand–foot skin reaction.

Appetite and body weight should be monitored regularly in patients receiving lenvatinib. In patients with decreased appetite or weight loss of grade 1 or 2 severity, dose reduction or interruption may be needed temporarily, and, if so, subsequently resumed at the same dose when symptoms have been alleviated.²³ If decreased appetite or weight loss of grade 3 severity occurs early during treatment, dose reduction or interruption may be required.²³ Patients can also be offered an antiemetic agent or oral nutrition²³; in our clinical experience, patients may also benefit from the use of an appetite-stimulating drug such as megestrol acetate.

Expert recommendations.

- Regularly monitor appetite and body weight.
- Temporary (grade 1 or 2) or longer term (grade 3) lenvatinib dose reduction or interruption may be required.
- Antiemetics, oral nutrition, or appetite stimulants may be helpful.

Fatigue. In the REFLECT study, fatigue was reported in 30% of patients in the lenvatinib group, with 4% of patients experiencing AEs of grade ≥ 3 severity.⁹ Dose interruption or dose reduction because of fatigue was required in 5.7% of patients in the lenvatinib group.¹⁰ Fatigue resulted in treatment discontinuation in seven patients (1.5%) in the lenvatinib group.¹⁰

Although fatigue is a common non-specific symptom in patients with advanced HCC, treatable causes of fatigue should be looked for during lenvatinib therapy. As an example, an association

between fatigue and a rise in thyroid stimulating hormone (TSH), weight loss/anorexia, or disease progression should be taken into consideration.³⁴ In the first instance, all potential causes of AEs need to be evaluated thoroughly by checking complete blood cell counts and TSH levels, prior to lenvatinib dose reduction/interruption (depending on AE severity).

Patients with grade 1 fatigue can be managed with rest and do not require dose interruption or adjustment.²³ A healthy and active lifestyle should be encouraged in patients receiving lenvatinib. Physical exercise has been shown to improve cancer-related fatigue effectively.^{43,44} In patients with grade ≥ 2 fatigue, lenvatinib treatment can be interrupted if symptoms are intolerable.²³ Once symptoms are alleviated, treatment can be resumed at the same dose (if fatigue had occurred later during treatment) or at a reduced dose (if fatigue had been reported early during treatment).²³

Expert recommendations.

- Initially, thoroughly evaluate all treatable causes of fatigue.
- For patients with grade ≥ 2 fatigue, interrupt lenvatinib treatment if symptoms are intolerable, resume at the same or a reduced dose once symptoms are alleviated.

Hepatic disorder/hepatotoxicity. Hepatotoxicity was common with lenvatinib in the REFLECT study, occurring in 47.7% of patients (grade ≥ 3 AEs 26.1%).¹⁰ The median time to the first hepatotoxic event was 6.4 weeks in patients receiving lenvatinib. The most common (incidence $\geq 5\%$) hepatotoxic

events in lenvatinib recipients were increased blood bilirubin (14.9%), increased aspartate aminotransferase (AST; 13.7%), increased alanine aminotransferase (ALT; 11.1%), hypoalbuminemia (9.2%), hepatic encephalopathy (8.0%), increased gamma-glutamyltransferase (GGT; 7.8%), and increased blood alkaline phosphatase (ALP; 6.7%). Grade 3 or 4 increases in laboratory parameters in lenvatinib recipients included increases in blood bilirubin (13.2%), ALT (7.9%), AST (12.1%), GGT (31.4%), and ALP (6.6%).¹⁰

Hepatic encephalopathy occurred in 8.4% of lenvatinib recipients; 5.5% of hepatic encephalopathy events in lenvatinib recipients were of grade ≥ 3 severity, and four patients had fatal events.¹⁰ Hepatic failure occurred in 3.6% of lenvatinib recipients; all hepatic failure events with lenvatinib were of grade ≥ 3 severity, and 12 patients had fatal events. Hepatotoxic events led to treatment discontinuation in 5.5% of patients in the lenvatinib group, dose interruption in 7.4%, and dose reduction in 12.2% of patients; 17 deaths (3.6%) in the lenvatinib group were because of hepatotoxicity AEs. The risk of developing hepatic encephalopathy or hepatic failure was higher in patients with worse hepatic impairment and/or tumor burden at baseline and in patients aged ≥ 75 years.¹⁰

Any underlying causes of hepatotoxicity (e.g. cirrhosis or hepatitis) need to be checked. Liver function tests should be performed prior to initiating lenvatinib therapy, and patients should be monitored regularly during treatment. Based on our clinical experience, we recommend that monitoring should occur every 2 weeks for the first month and monthly thereafter, and at every regular follow-up visit, depending on the judgment of the individual clinician. Importantly, to reduce the burden of testing on patients and clinics, monitoring intervals for AEs (e.g. proteinuria and hepatotoxicity) should be aligned.

Table 4 provides an overview of the management of hepatotoxicity during lenvatinib treatment. Lenvatinib treatment can be continued in patients who develop a tolerable grade 2 hepatotoxic event and in patients with ALT, AST, or GGT levels 10-fold lower than the normal range if considered appropriate.²³ In patients who develop an intolerable grade 2,²³ or grade 3 event,^{4,5,23} treatment should be interrupted and resumed at lower dosage (Table 1) after improvement in liver function is confirmed. Patients with non-life-threatening grade 4 hepatotoxic events can be managed in the same way as patients with grade 3 events; however, lenvatinib treatment should be permanently discontinued if hepatic failure occurs.^{4,5,23}

Expert recommendations.

- Lenvatinib treatment can be continued in patients who develop a tolerable grade 2 hepatotoxic event.
- Treatment should be interrupted for intolerable grade 2 or 3 events; after liver function improvement, resume lenvatinib at a lower dosage.
- Discontinue lenvatinib if hepatic failure occurs.

Hypothyroidism. Treatment with lenvatinib has been associated with hypothyroidism. In the REFLECT study, hypothyroidism occurred in 16% of patients receiving lenvatinib; no

grade ≥ 3 AEs were reported.⁹ Prior to initiating treatment in this study, 89.6% of patients in the lenvatinib group had TSH levels of less than or equal to the upper limit of normal.¹⁰ After treatment, TSH levels higher than the upper limit of normal were observed in 69.6% of lenvatinib recipients. Thyroid function should be monitored prior to initiating treatment, monthly during the first 2 months of treatment and regularly thereafter during treatment with lenvatinib.²³ Hypothyroidism, if detected, should be addressed with standard medical care to maintain euthyroid state.²³ However, based on our clinical experience, asymptomatic slight elevations in TSH levels do not necessarily require medical intervention for hypothyroidism. However, if TSH is > 10 mIU/L or is 5–10 mIU/L on two assays,^{45,46} we recommend consulting with an endocrinologist as thyroid replacement therapy may be necessary.

Expert recommendations.

- Monitor thyroid function prior to treatment, monthly during the first 2 months and regularly thereafter.
- Consult with an endocrinologist if TSH is > 10 mIU/L or 5–10 mIU/L on two assays.

Cardiovascular/cerebrovascular events. In the REFLECT study, cardiac dysfunction (including congestive cardiac failure, cardiogenic shock, and cardiopulmonary failure) occurred in 0.6% of lenvatinib recipients.¹⁰ Arterial thromboembolic events were reported in 2.3% of lenvatinib recipients (serious AEs in 10 patients), with the most frequent events being myocardial infarction (four events) and cerebral infarction (one events). Posterior reversible encephalopathy syndrome (PRES)/reversible posterior leukoencephalopathy syndrome (RPLS) of grade 2 severity occurred in one patient in the lenvatinib group.¹⁰

Patients on lenvatinib treatment should be monitored for clinical signs of cardiac decompensation.³⁴ If grade 3 cardiac dysfunction occurs, treatment should be interrupted and subsequently resumed at a lower dose once it resolves to grade 0–1 severity or baseline level; treatment should be discontinued for a grade 4 event.^{4,5} If PRES/RPLS of any grade occurs, treatment should be interrupted; treatment resumption can be considered if the event resolves to grade 0–1 severity. Following an arterial thromboembolic event, treatment with lenvatinib should be discontinued.^{4,5} In high-risk patients (e.g. those with coronary artery disease or heart failure), medications known to prolong QT interval, such as class Ia and III anti-arrhythmics, should be avoided where possible.³⁴ Prior to treatment initiation in these patients, echocardiography should be performed and cardiac troponin and natriuretic peptide levels measured; thereafter, patients should be monitored regularly with electrocardiograms.³⁴

Expert recommendations.

- Monitor patients for clinical signs of cardiac decompensation; interrupt lenvatinib (grade 3 cardiac dysfunction) then resume at a lower dose once grade 0–1 or baseline levels achieved. Discontinue lenvatinib if grade 4 symptoms occur.

Table 4 General recommendations for the management of hepatotoxicity during lenvatinib treatment

Liver function test (CTCAE ver. 5.0)		Recommended management during lenvatinib therapy
Baseline < ULN	Baseline > ULN	
ALT increased		(1) Continue treatment in patients who develop a tolerable grade 2 event. (2) In case of 10-fold decreases in ALT, AST, or GGT levels lower than the normal ranges, lenvatinib can be continued when the physician deems it appropriate. (3) For patients who develop an intolerable grade 2 event or a grade 3 event, resume treatment at a dose reduced by one dose level after an improvement in liver dysfunction is confirmed. (4) Patients with a non-life-threatening grade 4 event can be managed in the same way as patients with a grade 3 event. However, treatment should be permanently discontinued in patients who develop hepatic failure.
Grade 1: > ULN to 3.0 × ULN	Grade 1: 1.5 to 3.0 × BL	
Grade 2: > 3.0 to 5.0 × ULN	Grade 2: > 3.0 to 5.0 × BL	
Grade 3: > 5.0 to 20.0 × ULN	Grade 3: > 5.0 to 20.0 × BL	
Grade 4: > 20.0 × ULN	Grade 4: > 20.0 × BL	
AST increased		
Grade 1: > ULN to 3.0 × ULN	Grade 1: 1.5 to 3.0 × BL	
Grade 2: > 3.0 to 5.0 × ULN	Grade 2: > 3.0 to 5.0 × BL	
Grade 3: > 5.0 to 20.0 × ULN	Grade 3: > 5.0 to 20.0 × BL	
Grade 4: > 20.0 × ULN	Grade 4: > 20.0 × BL	
ALP increased		
Grade 1: > ULN to 2.5 × ULN	Grade 1: 2.0 to 2.5 × BL	
Grade 2: > 2.5 to 5.0 × ULN	Grade 2: > 2.5 to 5.0 × BL	
Grade 3: > 5.0 to 20.0 × ULN	Grade 3: > 5.0 to 20.0 × BL	
Grade 4: > 20.0 × ULN	Grade 4: > 20.0 × BL	
Blood bilirubin increased		
Grade 1: > ULN to 1.5 × ULN	Grade 1: > 1.0 to 1.5 × BL	
Grade 2: > 1.5 to 3.0 × ULN	Grade 2: > 1.5 to 3.0 × BL	
Grade 3: > 3.0 to 10.0 × ULN	Grade 3: > 3.0 to 10.0 × BL	
Grade 4: > 10.0 × ULN	Grade 4: > 10.0 × BL	
GGT increased		
Grade 1: > ULN to 2.5 × ULN	Grade 1: 2.0 to 2.5 × BL	
Grade 2: > 2.5 to 5.0 × ULN	Grade 2: > 2.5 to 5.0 × BL	
Grade 3: > 5.0 to 20.0 × ULN	Grade 3: > 5.0 to 20.0 × BL	
Grade 4: > 20.0 × ULN	Grade 4: > 20.0 × BL	

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyltransferase; ULN, upper limit of normal.

- Interrupt treatment if PRES/RPLS occurs (any grade); resume when severity resolves to grade 0–1.

Other adverse events

Dysphonia. Dysphonia is a known side effect of anti-angiogenic drugs.^{47–49} In the REFLECT study, dysphonia occurred in 24% of lenvatinib recipients, with < 1% of patients experiencing grade ≥ 3 dysphonia.⁹ The only treatment for dysphonia due to angiogenesis inhibitors is discontinuation of therapy.⁴⁷

Expert recommendation.

- As dysphonia is not life-threatening, therapy discontinuation must be weighed against the benefits of continued treatment.

Impaired wound healing. Although there is currently a lack of published clinical evidence, there are limited reports of impaired wound healing in patients receiving lenvatinib.¹⁰ Recently, updated guidance proposes withholding lenvatinib for at least 1 week prior to elective surgery and not administering lenvatinib for at least 2 weeks following major surgery and until adequate wound healing.⁴

Expert recommendation.

- As the safety of resuming lenvatinib after the resolution of wound healing complications has not been established, clinical decisions should be made after adequately considering the risks and benefits for each patient.

Osteonecrosis of the jaw. Although there is currently a lack of published clinical evidence, there are limited reports of osteonecrosis of the jaw (ONJ) in patients receiving lenvatinib.^{4,50} Factors that may increase the risk of jaw bone problems include concomitant use of bisphosphonates, denosumab, presence of dental disease, or undergoing an invasive dental procedure. Clinicians should perform an oral examination prior to, and periodically during, treatment with lenvatinib. Patients should be advised about good oral hygiene practices and, where possible, invasive dental procedures should be avoided during lenvatinib treatment, particularly in high-risk patients. If possible, lenvatinib should be stopped for at least 1 week prior to scheduled dental surgery or invasive dental procedures. For patients requiring invasive dental procedures, discontinuation of bisphosphonate treatment may reduce the risk of ONJ. If ONJ develops, lenvatinib should be withheld and restarted based on clinical judgment of adequate resolution.⁴

Expert recommendation.

- Monitor patients for clinical signs of ONJ, consider oral examination prior to, and periodically during, lenvatinib treatment.

Summary

Lenvatinib provides a significant survival benefit in patients with advanced HCC. However, it is associated with high rates of AEs, which may adversely affect clinical outcomes. Patients receiving lenvatinib should be advised about prophylactic measures and monitored regularly for AEs. Patients who develop AEs can be managed with lenvatinib dose interruption, adjustment or discontinuation of treatment. For mild or moderate (grade 1 or 2) AEs, dose interruption is generally not required, unless AEs are intolerable despite optimal management.^{4,5} For persistent or intolerable grade 2 or 3 AEs, lenvatinib treatment should be interrupted until symptoms improve/resolve to grade 0–1 or baseline levels. Thereafter, treatment should be resumed at the same or a lower dose.^{4,5} There have been reports suggesting that occurrence of some AEs may predict a survival benefit, and patients who discontinue lenvatinib treatment because of AEs may have a poor survival prognosis. Progression may occur in patients who do not initially respond to treatment or receive a suboptimal dose following dosage reduction, resulting in lack of efficacy. Therefore, to derive maximum treatment benefit and ensure long-term disease control, lenvatinib should be maintained at the highest possible dose when managing AEs.²³

Recently, immune checkpoint inhibitors have shown antitumor activity against HCC.^{51–55} The overall incidence of any treatment-related AEs tends to be higher in patients treated with multikinase inhibitors (93–95%) compared with PD-1 inhibitor monotherapy (61–74%).^{9,51,52,54,56,57} Treatment-related AEs of \geq grade 3 occurred more frequently with multikinase inhibitors than with PD-1 inhibitor monotherapy (49–57% vs 18–26%). Frequently reported treatment-related AEs \geq grade 3 with multikinase inhibitors were hand–foot skin reaction, hypertension, anorexia, weight loss, and proteinuria with an incidence of $>$ 5%, which are mostly symptomatic, but manageable.^{9,56} For PD-1 inhibitors, the most frequent treatment-related AEs were AST or ALT elevation with an incidence of 4–7%, which are usually asymptomatic.^{51,52,54} However, immune-related AEs, a unique spectrum of AEs associated with immune checkpoint inhibitors, may happen in some patients treated with immune checkpoint inhibitors. Immune-related AEs are generally manageable, but they are sometimes life-threatening.

To conclude, effective management of lenvatinib-associated AEs using prophylactic measures, regular monitoring and symptomatic management, can ensure continued treatment and maximum survival benefit in patients with advanced HCC receiving first-line lenvatinib therapy.

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[Correction added on 06 December 2021, after first online publication: references 46 and 56 have been swapped.]

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1 Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0.