Clinical impact of lenvatinib in patients with unresectable hepatocellular carcinoma who received sorafenib

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Background: Lenvatinib has been approved for use in the systemic treatment for unresectable hepatocellular carcinoma (HCC). This study aimed to investigate the efficacy and safety of lenvatinib in patients with unresectable HCC who received sorafenib.

Methods: A total of 40 patients who received lenvatinib after sorafenib were retrospectively identified: as second line in 20 patients, third line in 10 patients, and fourth line and later lines in 10 patients. The treatment response to lenvatinib was determined in accordance with the guidelines of the modified Response Evaluation Criteria in Solid Tumors (mRECIST) every 2-3 months after commencement of lenvatinib.

Results: Median progression-free survival (PFS) and median overall survival (OS) of the whole population were 3.3 and 9.8 months, respectively. The objective response rate was 27.5%. Univariate and multivariate analyses showed that alpha-fetoprotein level > 400 ng/mL was an independent prognostic factor of worse PFS and OS. The clinical outcomes of lenvatinib therapy as second-line, third-line, or fourth line and later line treatment were similar, and previous response to sorafenib could predict the response to subsequent lenvatinib. Most adverse events were grades 1–2, and the majority of patients tolerated the side effects. Our study confirms the efficacy and safety of lenvatinib as second-line and later line treatment for patients with unresectable HCC who received sorafenib in clinical practice.

1   **Clinical Impact of Lenvatinib in Patients with Unresectable Hepatocellular**

2   **Carcinoma Who Received Sorafenib**

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13   **Running title:** Lenvatinib in HCC

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34   **Abstract**

35   **Background:** Lenvatinib has been approved for use in the systemic treatment for unresectable

36   hepatocellular carcinoma (HCC). This study aimed to investigate the efficacy and safety of

37   lenvatinib in patients with unresectable HCC who received sorafenib.

38   **Methods:** A total of 40 patients who received lenvatinib after sorafenib were retrospectively

39   identified: as second line in 20 patients, third line in 10 patients, and fourth line and later lines in

40   10 patients. The treatment response to lenvatinib was determined in accordance with the

41   guidelines of the modified Response Evaluation Criteria in Solid Tumors (mRECIST) every 2-3

42   months after commencement of lenvatinib.

43   **Results:** Median progression-free survival (PFS) and median overall survival (OS) of the whole

44   population were 3.3 and 9.8 months, respectively. The objective response rate was 27.5%.

45   Univariate and multivariate analyses showed that alpha-fetoprotein level > 400 ng/mL was an

46   independent prognostic factor of worse PFS and OS. The clinical outcomes of lenvatinib therapy

47   as second-line, third-line, or fourth line and later line treatment were similar, and previous

48   response to sorafenib could predict the response to subsequent lenvatinib. Most adverse events

49   were grades 1–2, and the majority of patients tolerated the side effects. Our study confirms the

50   efficacy and safety of lenvatinib as second-line and later line treatment for patients with

51   unresectable HCC who received sorafenib in clinical practice.

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53   **Keywords:** lenvatinib; hepatocellular carcinoma; sorafenib; survival

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Introduction

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66   Hepatocellular carcinoma (HCC) is one of the most common aggressive malignancies

67   worldwide and is the second leading cause of cancer-related deaths in Taiwan. The well-known

68   risk factors for HCC include hepatitis B, hepatitis C, and alcoholic and nonalcoholic

69   steatohepatitis. Despite surveillance programs in high-risk patients, some patients with HCC

70   have advanced status when diagnosed, including multicentric intrahepatic spread, portal vein

71   thrombosis (PVT), huge tumor burden, and distant metastasis, contributing to poor prognosis

72   (Bertuccio et al. 2017; Bruix et al. 2016; Cabibbo et al. 2012).

73   Sorafenib is a small oral tyrosine and serine/threonine kinase inhibitor (TKI) that has been

74   proven as the first-line systemic treatment for unresectable HCC (Cheng et al. 2009; Llovet et al.

75   2008). Before 2018, sorafenib therapy is the only recommended strategy that can prolong overall

76   survival; apart from this, no other approved targeted therapy in the past 10 years has been

77   available as the first-line treatment for unresectable HCC (Cainap et al. 2015; Cheng et al. 2013;

78   Johnson et al. 2013). Recently, lenvatinib, a newly developed TKI targeting vascular endothelial,

79   fibroblast, and platelet-derived growth factor receptors, has become available as the first-line

80   treatment. The REFLECT trial showed that lenvatinib led to significantly better progression-free

81 survival (PFS), time to progression (TTP), and objective response rate (ORR) than sorafenib and

82 was non-inferior to sorafenib in terms of overall survival (OS) (Kudo et al. 2018). Since then, an

83 increasing number of patients have been receiving lenvatinib therapy as the first-line treatment in

84 many countries, especially in Japan and Taiwan.

85   In the SELECT trial, a study that focused on the use of lenvatinib in radioiodine-refractory

86 thyroid cancer, there was no significant difference in survival between patients who received and

87 did not receive sorafenib (Schlumberger et al. 2015). This phenomenon was also observed in

88 patients with HCC. Recently, only few studies have showed no difference in survival outcomes

89 between patients who received targeted therapy and treatment-naïve patients (Hiraoka et al.

90 2019a; Hiraoka et al. 2019b; Hiraoka et al. 2019c). However, to the best of our knowledge,

91 information on the clinical impact of lenvatinib, such as prognostic factors, adverse events, and

92 correlation between sorafenib and lenvatinib response, in patients with HCC who received

93 sorafenib is limited in literature. The present study aimed to investigate the clinical impact and

94 safety of lenvatinib in patients with HCC who received sorafenib, including prognostic factors of

95 PFS and OS, survival comparison between different treatment line, presentation of side effects,

96 and correlation of response of lenvatinib and prior sorafenib.

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111   **Materials & Methods**

112   *Patient selection*

113   Between September 2018 and December 2019, the records of patients with unresectable

114   HCC who underwent treatment at the Kaohsiung Chang Gung Memorial Hospital were reviewed

115   retrospectively. First, only patients who received sorafenib followed by lenvatinib were enrolled.

116   Second, the included patients must have had at least one measurable target lesion for the

117   evaluation of treatment response. Third, the eligible patients had an Eastern Cooperative

118   Oncology Group Performance Status score of 0–1 and controlled hypertension. We excluded

119   patients with a history of second primary malignancy or concurrent hepatocholangiocarcinoma.

120   Finally, 40 patients who had available medical records and follow-up visits were identified.

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122   *Diagnosis and staging of HCC*

123   The diagnosis of each patient with HCC was made according to pathology and dynamic

124   computed tomography (CT) or magnetic resonance imaging (MRI) of the liver in high risk

125   patients (HBV or HCV related liver cirrhosis) (Marrero et al. 2018; Omata et al. 2017). Staging

126   was determined according to the Barcelona Clinic Liver Cancer (BCLC) staging classification at

127   the time of lenvatinib treatment initiation (Llovet et al. 1999). Alpha-fetoprotein (AFP) was

128   measured before commencement of lenvatinib for each patient.

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130 *Lenvatinib treatment and assessment of adverse events*

131   Lenvatinib was orally administered at a dose of 10 mg and 8 mg once daily for patients with

132 body weight ≥ 60 kg and < 60 kg, respectively. Adverse events (AEs) were evaluated according

133 to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0,

134 and the worst grade for each AE was recorded.

135

136 *Evaluation of treatment response*

137   Each patient must have had at least one measurable target lesion and enhanced CT or MRI

138 of the liver to be evaluated for treatment response to lenvatinib in accordance with the guidelines

139 of the modified Response Evaluation Criteria in Solid Tumors (mRECIST) (Lencioni & Llovet

140 2010) every 2-3 months after commencement of lenvatinib. Assessment was performed

141 independently by two radiologists blinded to any information about the patients'

142 clinicopathologic features or prognosis.

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144 *Statistical analysis*

145   Statistical analyses were performed using SPSS 19 software (IBM, Armonk, NY, USA).

146   Statistical analyses of group differences were performed using the Chi-square test with

147   Bonferroni correction for categorical variables. PFS was defined as the time from the initiation

148   of lenvatinib treatment to disease progression or death from any cause, and OS was calculated

149   from the date of lenvatinib treatment initiation to death or last living contact.

150   Kaplan–Meier method was used to estimate PFS and OS, and the log-rank test was

151   performed to evaluate the differences between groups for univariate analysis. The hazard ratio

152   (HR) with 95% confidence interval (CI) and P-values were calculated to quantify the strength of

153   the associations between the prognostic parameters and survival. Cox proportional hazards

154   model was performed for multivariate analysis. All tests were two sided, and a P-value of less

155   than 0.05 was considered to indicate statistical significance.

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157   *Ethics statement*

158   This retrospective study was approved by the Chang Gung Medical Foundation Institutional

159   Review Board (201900611B0). All methods were performed in accordance with the approved

160   guidelines, and written informed consent was waived by the Chang Gung Medical Foundation

161   Institutional Review Board.

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173   **Results**

174   *Patient characteristics*

175   We identified 40 patients with unresectable HCC who received lenvatinib as second-line or

176   later line treatment at our institution between September 2018 and December 2019. There were

177   35 men and 5 women with a mean age of 58 (range, 34–78) years. All patients had liver cirrhosis

178   in our study. The Child–Pugh classification was A in 31 (77.5%) patients and B in 9 (22.5%)

179   patients, whereas the BCLC staging classification was B in 3 (7.5%) patients and C in 37

180   (92.5%) patients. Regarding viral hepatitis, 29 (72.5%) patients had hepatitis B virus (HBV)

181   infection, 7 (17.5%) patients had hepatitis C virus (HCV) infection, and 4 (10.0%) were negative

182   for HBV or HCV. Nineteen (47.5%) patients had macrovascular invasion, including 11 patients

183   (27.5%) with main PVT. In addition, 24 (60.0%) patients underwent hepatectomy before

184   lenvatinib treatment, and extrahepatic spread was noted in 32 (80.0%) patients. There were 17

185   (42.5%) patients with AFP > 400 ng/mL. At the time of analysis, the median period of follow-up

186   was 15.1 months for the 15 survivors and 8.9 months for all 40 patients. The clinicopathologic

187   parameters of the patients are shown in Table 1.

188

189   *Clinical outcomes of lenvatinib treatment*

190   The median PFS of the whole population was 3.3 months (Figure 1A). Regarding PFS,

191   univariate analysis showed no significant differences in all parameters except AFP > 400 ng/mL.

192   The 17 patients with AFP > 400 ng/mL had worse PFS as compared to the 23 patients with AFP

193   < 400 ng/mL (2.7 months versus 4.2 months, P = 0.020, Figure 2A). Multivariate analysis

194   revealed that AFP < 400 ng/mL (P = 0.024; HR, 0.46; 95% CI, 0.23–0.90) was an independent

195   prognostic factor for better PFS.

196   Regarding OS, the median OS of the whole population was 9.8 months (Figure 1B). No

197   significant differences were observed in terms of all parameters except AFP > 400 ng/mL in the

198   univariate analysis. As expected, a superior OS was found in 23 patients with AFP < 400 ng/mL

199   when compared with the other 17 patients with AFP > 400 ng/mL (not reached versus 6.1

200   months, P < 0.001, Figure 2B). According to the multivariate analysis, AFP < 400 ng/mL (P <

201   0.001; HR, 0.19; 95% CI, 0.08–0.46) was an independent prognostic factor for superior OS. The

202   results of univariate and multivariate analyses of PFS and OS in 40 patients with unresectable

203   HCC who received lenvatinib after failure of sorafenib treatment are shown in Tables 2 and 3.

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205   *Response and survival*

206   The response to lenvatinib treatment was determined according to the mRECIST criteria,

207   including 1 (2.5%) patient with complete response (CR), 10 (25.0%) with partial response (PR),

208   16 (40.0%) with stable disease (SD), and 13 (32.5%) with progressive disease (PD). The 6-

209   month PFS rates were 45.7% and 18.8% in the PR and SD groups, respectively; the 1-year OS

210   rates were 53.3% in the PR group, 55.6% in the SD group, and 8.5% in the PD group.

211   In our study, lenvatinib therapy was used as second-line treatment in 20 (50.0%) patients,

212   third-line treatment in 10 (25.0%) patients, and fourth-line and later lines in 10 (25.0%) patients.

213   The median PFS and OS were 3.1 months and 8.1 months, respectively, for the second-line

214   treatment; 3.7 months and 11.5 months for the third-line treatment; and 3.1 months and 12.0

215   months for the fourth line and later line treatments. The results of the survival analyses of the

216   treatment effects of lenvatinib are shown in Table 4.

217   We also analyzed the correlation of treatment responses between sorafenib and lenvatinib.

218   There were 6 patients with PR to sorafenib previously, and they all achieved CR or PR with

219   lenvatinib treatment. Among 20 patients with SD in response to sorafenib treatment, only 4

220   (20%) had PR to lenvatinib treatment, and most patients (the other 16 patients, 80%) remained

221   stable with lenvatinib treatment. Among 14 patients who had disease progression with sorafenib

222   treatment, only 1 (7.1%) had PR to lenvatinib treatment, and the other 13 patients showed poor

223   response to lenvatinib treatment. A comparison of treatment response between sorafenib and

224   lenvatinib is presented in Table 5.

225

226   *Adverse events associated with lenvatinib*

227   The AEs of lenvatinib treatment were informed to most patients. AEs with higher

228   frequencies (> 20%) included hypertension, diarrhea, decreased appetite, fatigue, and palmar-

229   plantar erythrodysesthesia. Most AEs were grade 1–2; grade 3–4 toxicities were rare, including

230   hypertension (12.5%), diarrhea (2.5%), decreased appetite (2.5%), and fatigue (2.5%). The

231   majority of the patients tolerated the side effects of lenvatinib treatment, and no patients had

232   treatment-related deaths. The profiles of these AEs are shown in Table 6.

233

234   **Discussion**

235   HCC is an extremely aggressive malignant cancer, and its treatment is extremely

236   challenging with advanced tumor status. For the past 10 years, sorafenib therapy has been the

237   only recommended first-line systemic treatment for unresectable HCC (Cheng et al. 2009; Llovet

238 et al. 2008). Although several clinical trials were conducted with several compounds that were

239 designed to be superior or non-inferior to sorafenib, all of them failed, and none were approved

240 (Cainap et al. 2015; Cheng et al. 2013; Johnson et al. 2013). Recently, the REFLECT trial

241 showed that lenvatinib therapy is non-inferior to sorafenib in terms of OS (Kudo et al. 2018).

242 Subsequently, lenvatinib was used as the first-line treatment for unresectable HCC in some

243 countries, especially in Japan, and several real-world studies demonstrated that lenvatinib

244 treatment yields good response and has safety (Hiraoka et al. 2019a; Hiraoka et al. 2019b; Obi et

245 al. 2019). However, the clinical impact of lenvatinib treatment in patients who received sorafenib

246 treatment remains limited. In our study, the PFS and OS were 3.3 and 9.8 months, respectively,

247 in patients who received lenvatinib after sorafenib; the outcome was similar to that of other

248 second-line treatments for HCC in the previous phase III trials (Bruix et al. 2017; Zhu et al.

249 2019). In addition, AFP > 400 ng/mL was noted as an independent poor prognostic factor of PFS

250 and OS in univariate and multivariate analyses.

251   In the REFLECT trial, patients with Child–Pugh classification B or main PVT were

252 excluded; thus, the efficacy and safety of lenvatinib for these patients are still unclear. However,

253 some patients who had Child–Pugh classification B or main PVT are still treated with lenvatinib

254   in real-world practice. In our study, we enrolled 9 (22.5%) patients with Child–Pugh

255   classification B and 11 (27.5%) patients with main PVT who received lenvatinib therapy as

256   systemic treatment. The median PFS and OS were worse in patients with Child–Pugh

257   classification B or main PVT than in those in patients with Child–Pugh classification A or non-

258   main PVT, although the difference was not significant. This effect was also observed in 19

259   (47.5%) patients with macrovascular invasion. In contrast, patients who underwent hepatectomy

260   before lenvatinib treatment had better PFS than those who did not, although there was no

261   significant difference. However, the benefit of OS was marginally significant in the hepatectomy

262   group than in the non-hepatectomy group. This could be due to the small size of the patient

263   population in our study.

264   Sorafenib and lenvatinib have been used in first-line systemic treatment for unresectable

265   HCC, and patients who received lenvatinib as second-line or later line treatment were not

266   enrolled in the REFLECT trial. However, some patients may have received other therapeutic

267   modalities before lenvatinib treatment in clinical practice, such as sorafenib therapy, hepatic

268   arterial infusion chemotherapy, or immunotherapy; thus, lenvatinib therapy is used as second-

269   line or later line treatment rather than first-line treatment. In our study, the median PFS and OS

270   were similar among the second-line, third-line, and fourth-line and later line treatments, although

271   the OS of the second-line treatment was mildly worse than that of the third-line and later line

272   treatments, indicating the efficacy of lenvatinib as second-line and later line treatments for

273   unresectable HCC.

274   The response rate is also an important issue in HCC treatment. Our study showed that the

275   median PFS was better in responders than in patients with SD or PD, but the 1-year OS rate was

276   equal between patients with PR or SD. In addition, the response to previous sorafenib could

277   predict the response of subsequent lenvatinib. In our study, all patients who responded to

278   sorafenib had treatment response to lenvatinib; most patients (80%) with SD as a response to

279   sorafenib treatment remained in a stable condition with lenvatinib treatment. Patients without

280   response to sorafenib were still not found to be responsive to lenvatinib (92.9%). The correlation

281   between treatment response to sorafenib and lenvatinib is extremely helpful in the treatment of

282   HCC in clinical practice.

283   Our study had several limitations. First, the study had a retrospective design, with a small

284   sample size, and all patients were treated at a single institution. Second, the number of female

285   patients in our study was limited; therefore, a bias of patient sex might have existed. Third, the

286   follow-up period may not be adequately long, and some survival benefit may not be significant.

287   However, to the best of our knowledge, this is the first study designed to investigate the clinical

288   impact of lenvatinib as second-line and later line treatment in patients with unresectable HCC

289   who received sorafenib. Further studies with a larger population or a randomized controlled trial

290   are warranted to validate the findings of this study.

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295   **Conclusions**

296   Our study confirms the efficacy and safety of lenvatinib for use as second-line and later line

297   treatment for patients with unresectable HCC who received sorafenib in clinical practice.

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Competing interests

The authors declare that they have no competing interests.

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Authors' Contributions

YHC conceived and designed the experiments. YYC wrote the main manuscript text. CCW

and YWL performed the experiments. WFL prepared the tables and figures. All authors

reviewed the manuscript.

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329   **Figure Legends**

330   **Figure 1.** Kaplan–Meier survival curves of progression-free survival (PFS) and overall survival

331   (OS) among patients with unresectable hepatocellular carcinoma who received lenvatinib

332   treatment as second-line or later line treatment. (A) PFS and (B) OS.

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334   **Figure 2.** Comparison of survival curves of progression-free survival (PFS) and overall survival

335   (OS) between patients with unresectable hepatocellular carcinoma who had AFP > 400 ng/mL or

336   AFP < 400 ng/mL. (A) PFS and (B) OS.

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345   **Reference**

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Characteristics of 40 patients with unresectable hepatocellular carcinoma who received lenvatinib after failure of sorafenib

Table 1. Characteristics of 40 patients with unresectable hepatocellular carcinoma who received lenvatinib after failure of sorafenib

Characteristics	
Age (median)	58 years (34-78)
Body weight	66.2 kg (44.8-109.5)
Liver cirrhosis	40 (100%)
ECOG performance status	
0	6 (15.0%)
1	34 (85.0%)
Sex	
Male	35 (87.5%)
Female	5 (12.5%)
Child–Pugh classification	
A	31 (77.5%)
B	9 (22.5%)
BCLC classification	
B	3 (7.5%)
C	37 (92.5%)
Viral hepatitis status	
Hepatitis B	29 (72.5%)
Hepatitis C	7 (17.5%)
No	4 (10.0%)
Main portal vein thrombosis	
Yes	11 (27.5%)
No	29 (72.5%)
Macrovascular invasion	
Yes	19 (47.5%)
No	21 (52.5%)
Hepatectomy before lenvatinib	
Yes	24 (60.0%)
No	16 (40.0%)
Extrahepatic spread	
Yes	32 (80.0%)
No	8 (20.0%)
AFP > 400	
Yes	17 (42.5%)
No	23 (57.5%)

ECOG: Eastern Cooperative Oncology Group; BCLC: Barcelona-Clinic Liver Cancer

Univariate and multivariate analyses of PFS in 40 patients with unresectable hepatocellular carcinoma who received lenvatinib after failure of sorafenib

Table 2. Univariate and multivariate analyses of PFS in 40 patients with unresectable hepatocellular carcinoma who received lenvatinib after failure of sorafenib

Characteristics	No. of patients	Univariate		Multivariate	
		Median PFS (months)	P value	HR (95% CI)	P value
Age					
< 60 years	22 (55.0%)	3.2	0.40		
≥ 60 years	18 (45.0%)	3.4			
ECOG performance status					
0	6 (15.0%)	2.7	0.70		
1	34 (85.0%)	3.3			
Sex					
Male	35 (87.5%)	3.5	0.22		
Female	5 (12.5%)	2.9			
Child–Pugh classification					
A	31 (77.5%)	3.5	0.31		
B	9 (22.5%)	2.9			
BCLC staging classification					
B	3 (7.5%)	8.2	0.22		
C	37 (92.5%)	3.3			
Hepatitis B					
Yes	29 (72.5%)	5.6	0.26		
No	11 (27.5%)	3.2			
Hepatitis C					
Yes	7 (17.5%)	3.3	0.30		
No	33 (82.5%)	6.7			
Main portal vein thrombosis					

Yes	11 (27.5%)	3.1	0.53		
No	29 (72.5%)	3.7			
Macrovascular invasion					
Yes	19 (47.5%)	2.9	0.99		
No	21 (52.5%)	3.5			
Hepatectomy before lenvatinib treatment					
Yes	24 (60.0%)	3.4	0.62		
No	16 (40.0%)	2.9			
Extrahepatic spread					
Yes	32 (80.0%)	3.1	0.27		
No	8 (20.0%)	4.6			
AFP level > 400					
Yes	17 (42.5%)	2.7	0.020*		
No	23 (57.5%)	4.2		0.46 (0.23–0.90)	0.024*

HR: hazard ratio; CI: confidence interval; ECOG: Eastern Cooperative Oncology Group; PFS: progression-free survival; BCLC: Barcelona Clinic Liver Cancer. *Statistically significant.

Univariate and multivariate analyses of OS in 40 patients with unresectable hepatocellular carcinoma who received lenvatinib after failure of sorafenib

Table 3. Univariate and multivariate analyses of OS in 40 patients with unresectable hepatocellular carcinoma who received lenvatinib after failure of sorafenib

Characteristics	No. of patients	Univariate		Multivariate	
		Median OS (months)	P value	HR (95% CI)	P value
Age					
< 60 years	22 (55.0%)	12.0	0.93		
≥ 60 years	18 (45.0%)	9.8			
ECOG performance status					
0	6 (15.0%)	16.4	0.34		
1	34 (85.0%)	8.4			
Sex					
Male	35 (87.5%)	11.5	0.48		
Female	5 (12.5%)	3.5			
Child–Pugh classification					
A	31 (77.5%)	11.5	0.99		
B	9 (22.5%)	8.1			
BCLC staging classification					
B	3 (7.5%)	16.4	0.74		
C	37 (92.5%)	9.8			
Hepatitis B					
Yes	29 (72.5%)	NR	0.23		
No	11 (27.5%)	8.4			
Hepatitis C					
Yes	7 (17.5%)	9.8	0.16		
No	33 (82.5%)	NR			
Main portal vein thrombosis					

Yes	11 (27.5%)	12.0	0.53		
No	29 (72.5%)	8.1			
Macrovascular invasion					
Yes	19 (47.5%)	12.0	0.13		
No	21 (52.5%)	6.2			
Hepatectomy before lenvatinib treatment					
Yes	24 (60.0%)	13.1	0.09		
No	16 (40.0%)	6.7			
Extrahepatic spread					
Yes	32 (80.0%)	9.8	0.20		
No	8 (20.0%)	NR			
AFP leel > 400					
Yes	17 (42.5%)	6.1	<0.001*		
No	23 (57.5%)	NR		0.19 (0.08–0.46)	<0.001*

HR: hazard ratio; CI: confidence interval; ECOG: Eastern Cooperative Oncology Group; OS: overall survival; BCLC: Barcelona Clinic Liver Cancer; NR: not reach.*Statistically significant.

Survival analyses of the 40 patients with HCC who received lenvatinib after failure of sorafenib

Table 4. Survival analyses of the 40 patients with HCC who received lenvatinib after failure of sorafenib

Response to lenvatinib	Number of patients	6-month PFS rate (%)	P value	1-year OS rate (%)	P value
Complete response	1 (2.5%)				
Partial response	10(25.0%)	45.7		53.3	
Stable disease	16 (40.0%)	18.8	0.046*	55.6	0.20
Progressive disease	13 (32.5%)	0		8.5	

Lenvatinib treatment lines	Number of patients	PFS (months)	P value	OS (months)	P value
Second line	20 (50.0%)	3.1		8.1	
Third line	10 (25.0%)	3.7	0.38	11.5	0.98
Fourth line and later lines	10 (25.0%)	3.1		12.0	

HCC: hepatocellular carcinoma; PFS: progression-free survival; OS: overall survival; *Statistically significant.

Comparison of treatment response to sorafenib and lenvatinib in the 40 patients with HCC

Table 5. Comparison of treatment response to sorafenib and lenvatinib in the 40 patients with HCC

Response to lenvatinib	CR and PR	SD	PD	P value
Response to previous sorafenib				
PR (N=6)	6 (100%)	0 (0%)	0 (0%)	
SD (N=20)	4 (20%)	16 (80%)	0 (0%)	P<0.001*
PD (N=14)	1 (7.1%)	0 (0%)	13 (92.9%)	

HCC: hepatocellular carcinoma; CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; *Statistically significant.

Treatment-related adverse events of the 40 patients with unresectable hepatocellular carcinoma receiving lenvatinib after failure of sorafenib

Table 6. Treatment-related adverse events of the 40 patients with unresectable hepatocellular carcinoma receiving lenvatinib after failure of sorafenib

Adverse event	All patients (N=40)		Second line (N=20)		Third line (N=10)		Fourth and later line (N=10)	
	Any grades	Grade 3/4	Any grades	Grade 3/4	Any grades	Grade 3/4	Any grades	Grade 3/4
Hypertension	19 (47.5%)	5 (12.5%)	9 (45.0%)	3 (15.0%)	6 (60.0%)	1 (10.0%)	4 (40.0%)	1 (10.0%)
Diarrhea	14 (35.0%)	1 (2.5%)	6 (30.0%)	0 (0%)	4 (40.0%)	1 (10.0%)	4 (40.0%)	0 (0%)
Decreased appetite	9 (22.5%)	1 (2.5%)	4 (20.0%)	1 (5.0%)	3 (30.0%)	0 (0%)	2 (20.0%)	0 (0%)
Decreased body weight	7 (17.5%)	0 (0%)	4 (20.0%)	0 (0%)	1 (10.0%)	0 (0%)	2 (20.0%)	0 (0%)
Fatigue	11 (27.5%)	1 (2.5%)	7 (35.0%)	1 (5.0%)	2 (20.0%)	0 (0%)	2 (20.0%)	0 (0%)
Palmar-plantar erythrodysesthesia	8 (20.0%)	0 (0%)	3 (15.0%)	0 (0%)	3 (30.0%)	0 (0%)	2 (20.0%)	0 (0%)
Nausea	6 (15.0%)	0 (0%)	3 (15.0%)	0 (0%)	2 (20.0%)	0 (0%)	1 (10.0%)	0 (0%)
Vomiting	2 (5.0%)	0 (0%)	1 (5.0%)	0 (0%)	1 (10.0%)	0 (0%)	0 (0%)	0 (0%)
Skin rash	3 (7.5%)	0 (0%)	1 (5.0%)	0 (0%)	1 (10.0%)	0 (0%)	1 (10.0%)	0 (0%)

Figure 1

Survival outcome of lenvatinib as second-line or later line treatment.

Kaplan–Meier survival curves of progression-free survival (PFS) and overall survival (OS) among patients with unresectable hepatocellular carcinoma who received lenvatinib treatment as second-line or later line treatment. (A) PFS and (B) OS.
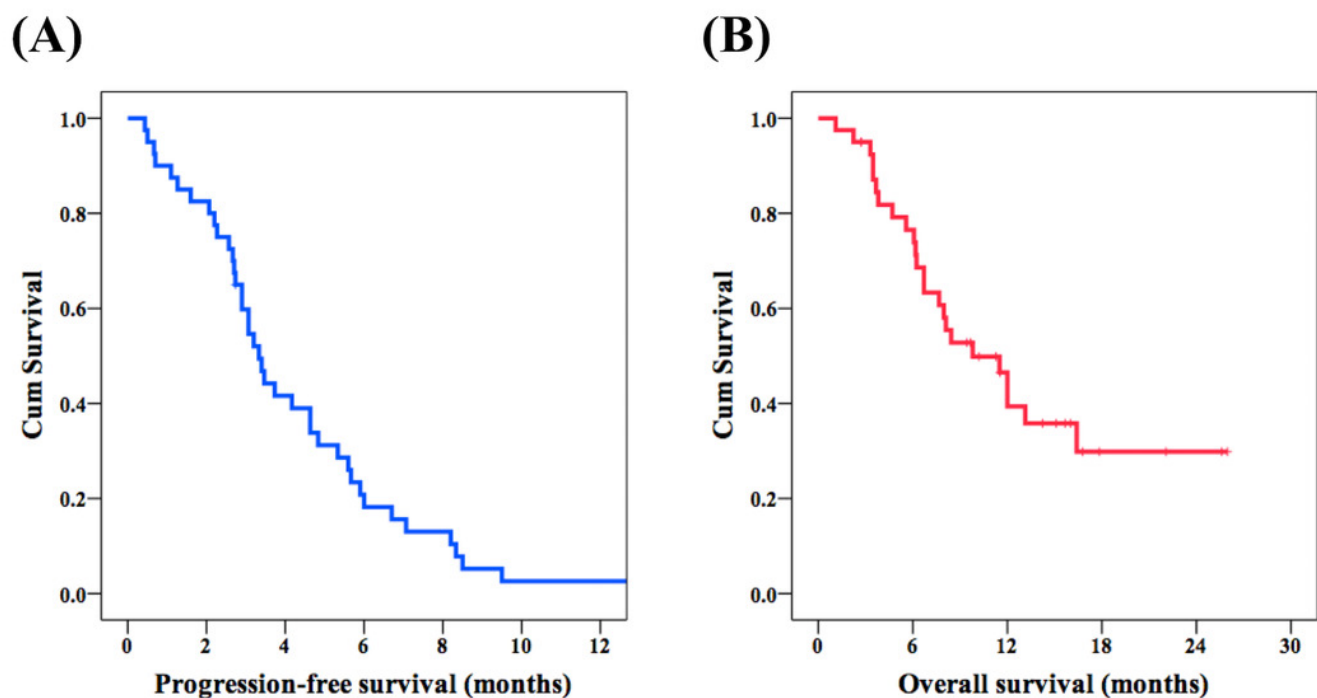
Figure 2

Correlation of AFP level and survival outcome.

Comparison of survival curves of progression-free survival (PFS) and overall survival (OS) between patients with unresectable hepatocellular carcinoma who had AFP > 400 ng/mL or AFP < 400 ng/mL. (A) PFS and (B) OS.