Efficacy of early clinical evaluation of lenvatinib therapy

[Original article]

Title: Reduction in tumor stain at 2 weeks after treatment initiation is a predictor of the efficacy of lenvatinib in patients with unresectable hepatocellular carcinoma

Short title: Efficacy of early clinical evaluation of lenvatinib therapy

Authors: Hideo Kunimoto[1,2], Satoshi Shakado[1], Takashi Tanaka[1], Kazuhide Takata[1], Ryo Yamauchi[1], Hiromi Fukuda[1], Naoaki Tsuchiya[1], Keiji Yokoyama[1], Daisuke Morihara[1], Yasuaki Takeyama[1], Fumihito Hirai[1], Shotaro Sakisaka[1]

[1] Department of Gastroenterology, Faculty of Medicine, Fukuoka University, Fukuoka, Japan.

[2] Department of Hepatology, Nagano Municipal Hospital, Nagano, Japan.

Corresponding author: Hideo Kunimoto, M.D.

Affiliation: Department of Gastroenterology, Faculty of Medicine, Fukuoka University, Fukuoka, Japan.

Address: 7-45-1 Nanakuma, Jonan-ku, Fukuoka 814-0180, Japan.

e-mail address: hideokunimoto@yahoo.co.jp

Telephone number: +81-92-801-1011 (Japan)

Facsimile number: +81-92-874-2663 (Japan)

KEY WORDS: lenvatinib, hepatocellular carcinoma, early clinical response

This manuscript consists of 15 pages of text (including these title pages).

Efficacy of early clinical evaluation of lenvatinib therapy

ABSTRACT

Background and Aims: Lenvatinib is an oral anticancer drug for patients with unresectable advanced hepatocellular carcinoma (HCC). We evaluated whether a reduction in tumor stain at 2 weeks after lenvatinib treatment in patients with unresectable HCC is a predictor of early treatment efficacy at 12 weeks.

Patients and Methods: Of the 23 patients who initiated lenvatinib treatment between April 2018 and January 2019, treatment efficacy was measured in 15 patients for more than 12 weeks after treatment. Changes in tumor stain, tumor size on contrast-enhanced computed tomography (CT), and serum levels of tumor markers were evaluated 2 weeks after lenvatinib treatment. Therapeutic efficacy was assessed by tumor stain and tumor size by contrast-enhanced CT within the first 12 weeks, according to the modified Response Evaluation Criteria in Solid Tumors (mRECIST) guidelines.

Results: At 12 weeks, efficacy evaluation of 15 patients revealed that 11 of them experienced partial responses, for a response rate of 73.3%. In the first 2 weeks, 13 patients (86.7%) experienced a decreased tumor stain, including 10 responders (90.9%) and 3 non-responders (75.0%). All patients in the non-responders group had required lenvatinib dose reduction due to adverse events within 12 weeks. On contrast-enhanced CT, the change rate of tumor stain to HCC at 2 weeks after treatment was <0.8 among 10 responders (90.9%) and 1 non-responder (25.0%; $p = 0.033$). No significant differences between responders and non-responders were observed with regard to most characteristics at baseline and at 2 weeks after treatment initiation. However, significant differences were observed between groups in the presence or absence of a dose suspension period, the presence or absence of lenvatinib dose reduction from the maximum value during the first 2 weeks, and decreased tumor stain at 2 weeks after treatment initiation.

Conclusion: Reduction in tumor stain at 2 weeks after lenvatinib treatment may be an early

biomarker of efficacy at 12 weeks in patients with unresectable HCC.

(314 words)

Efficacy of early clinical evaluation of lenvatinib therapy

Introduction

The death rate due to hepatocellular carcinoma (HCC) in Japan is the second largest among WHO member countries; thus, improved understanding of HCC disease measures is important in Japan [1]. In typical HCC cases, dynamic contrast-enhanced computed tomography (CE-CT) shows high absorption in the early arterial phase and low absorption in the portal phase [2]. The efficacy of recently introduced tyrosine kinase inhibitors (TKIs) has resulted in sporadic cases in which tumor staining has disappeared on CE-CT, but the tumor size has not changed.

The modified Response Evaluation Criteria in Solid Tumors (mRECIST) were proposed by Lencioni et al. to evaluate the diameter of tumor-stained areas on CE-CT in 2010 [3]. In HCCs characterized by hyperemia, disappearance of tumor density is considered to represent disappearance of viable tumor. In the treatment of HCC, in which tumor stain evaluation is critical, assessment of tumor staining is extremely appropriate.

Patients with advanced HCC that cannot be cured with conventional therapies have previously lacked effective treatment options, which changed with the introduction of multitargeted TKIs. In the pivotal Phase 3 lenvatinib mesylate (hereinafter called lenvatinib) trial, the median time to objective response was 2 months (95% confidence interval [CI]: 1.9 to 3.5), indicating rapid tumor shrinkage [4]. The phenomenon of immediate tumor shrinkage is known as early tumor shrinkage, and is associated with clinical outcomes in patients with other malignancies. However, it remains unknown when lenvatinib-induced tumor shrinkage begins.

Lenvatinib treatment has been reported to be associated with some serious adverse events (SAEs), the appearance of which causes a decline in patient QOL. Early imaging assessment appears to be very important for preventing SAEs resulting from lenvatinib treatment. In a previous study, we retrospectively examined the timing of lenvatinib-induced tumor shrinkage. However, the specific point within the 4-12–week period at which lenvatinib starts to shrink tumors remains unclear, because in many trials, initial imaging evaluation is

performed 4-12 weeks after treatment. Kuzuya et al. showed that changes in tumor stain on CE-CT, alpha fetoprotein (AFP) levels, and remnant liver function after 2 weeks of sorafenib therapy may be useful for predicting outcomes and anti-tumor response to sorafenib in patients with advanced HCC [5].

Based on these results, we conducted a prospective study to investigate the hypothesis that clinical changes (i.e., changes in tumor staining and AFP level) in the early post-dose period (i.e., 2 weeks post-dose) of lenvatinib therapy are useful indicators of therapeutic response. In this study, we evaluated whether a reduction in tumor stain 2 weeks after lenvatinib treatment in patients with unresectable HCC may be a predictor of early treatment efficacy at 12 weeks.

Patients and Methods

Patients

From April 2018 to March 2019, 170 patients with HCC admitted to our institution (Fukuoka University Hospital) underwent various treatments for HCC, including resection, radiofrequency ablation (RFA), hepatic artery embolization (TACE), radiation therapy, systemic chemotherapy, and best supportive care (BSC). Of the 170 patients with HCC who were treated, 23 (13.5%, n=170) patients received lenvatinib treatment (Figure 1). All 23 patients (18 men and 5 women) were diagnosed with HCC and underwent lenvatinib treatment at our hospital. These patients were required to stay in the hospital for a minimum of 2 weeks after treatment imitation. Five patients were lost to follow-up within 6 weeks, four patients had HCC without contrast effect, and one patient had difficulty with imaging assessment due to contrast agent allergy. The remaining 15 patients (13 men and 2 women) were enrolled in the present analysis. Retrospective demographic baseline (ie, at the time of initial lenvatinib treatment) data of theses 15 patients are shown in Table 1. The median age was 71 years (range, 55-85 years), and the median body weight was 55.4 kg (range, 43.5-69.8 kg). Six patients had chronic hepatitis C and nine patients had cirrhosis. A variety of adverse events (AEs), both in type and grade, occurred during the observation period in all 15 patients.

Medication

Although lenvatinib was prescribed at 8 mg/day or 12 mg/day depending on body weight based on the appropriate use guide for most patients, 4 mg/day or 8 mg/day was prescribed for some patients in consideration of patient background (Table 2). Most patients required dose interruption and dose reduction due to AEs, and the median day of initial dose reduction was day 38 (range, 4-306 days). By 8 weeks after treatment initiation, the median dose of lenvatinib was 8 mg/day (range, 0-12 mg/day). AEs were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0, and protocol-directed dose interruptions and dose

reductions were applied.

Follow-up

Over the follow-up period from April 2018 to March 2019, no patients were lost to follow-up. After initial lenvatinib treatment, the median follow-up period was 190 days (range, 83-330 days). Follow-up consisted of regular outpatient visits during which blood testing (including biochemical tests such as determination of levels of the tumor markers AFP and des-gamma-carboxy prothrombin [DCP]) was conducted at 2-4 week intervals. Imaging was performed at 2 weeks and 12 weeks after initiation of lenvatinib treatment. Imaging was performed at 1-3–month intervals after the first 2 weeks of lenvatinib treatment, and consisted of evaluation of images acquired during the arterial dominant phase of multiphasic CE-CT.

Data collection

Blood and biochemical data were evaluated at the start of lenvatinib therapy and at 2 weeks after treatment initiation. Albumin level, total bilirubin, and prothrombin time were measured as indicators of liver function. Data regarding tumor factors, including tumor size, tumor number, tumor differentiation status, and vascular invasion, were collected at initial HCC diagnosis. Using Image J software (National Institutes of Health, USA), the area of the tumor-stained region at the tumor's maximum diameter was measured by CE-CT before and 2 weeks after treatment, and the ratio of these two measurements was determined. A decrease in blood flow of ≥20% was defined as "with a decrease in blood flow."

Statistical analysis

All data were analyzed for normality and are reported as median (range) values. Nonparametric procedures were employed for analysis of background clinical parameters, and included the Mann-Whitney U-test. The χ^2 test was used for comparisons between groups for

factors such as liver function and tumor markers. *P*-values <0.05 were considered significant. Data were analyzed using SPSS software, ver. 16.0 (SPSS Inc., Chicago, IL, USA). As mentioned above, CT images were analyzed using Image J software.

Results

Evaluation of lenvatinib antitumor efficacy using mRECIST

The first evaluation of lenvatinib therapeutic efficacy using CE-CT was performed in all 15 patients 12 weeks after treatment initiation. Therapeutic efficacy was determined based on mRECIST. Of the 8 excluded patients not evaluated by mRECIST, 3 patients had tumor markers reduced and 5 patients had tumor markers elevated. No complete responses (CRs) were observed; 11 patients experienced a partial response (PR), no patients experienced stable disease (SD), and 4 patients experienced progressive disease (PD), for an overall response rate (ORR) of 73% and a disease control rate (DCR) of 73%.

Rate of change in tumor stain to HCC after lenvatinib treatment

Changes in tumor stain after treatment initiation in all 15 patients are shown in Figure 2. The tumor stain was reduced in most patients 2 weeks after treatment initiation. Only 2 patients experienced an increased tumor stain within the tumor, 1 of whom was started on lenvatinib 4 mg/day due to concerns about AEs. After increasing the lenvatinib dose to 8 mg/day after 2 weeks, the tumor stain decreased. Of the 13 patients with a decreased tumor stain at 2 weeks, the tumor stain continued to diminish in 10 patients (76.9%).

The responders group included patients with PR at 12 weeks, while the non-responders group included patients with PD. In the responders group, the tumor stain decreased in 10 patients (90.9%) after 2 weeks. One patient experienced a continued tumor stain increase after 2 weeks. In contrast, in the non-responders group, the tumor stain decreased in 3 patients (75.0%) after 2 weeks. Thus, 11 (73%) of the 15 patients continued to experience tumor stain changes that were consistent with the initial changes observed at 2 weeks. The rate of tumor stain changes at 2 weeks was significantly lower in the response group than in the non-responders group ($p < 0.05$) (Figure 3).

Comparison of maximum tumor diameter after lenvatinib treatment in responders and non-responders

Change in tumor size 2 weeks after initiation of lenvatinib treatment is shown in Figure 4. At 2 weeks after initiation of lenvatinib treatment, 6 cases of tumor growth and 9 cases of tumor shrinkage were observed. Of the 6 cases with increased tumor, tumor size continued to increase thereafter in 1 case (16.7%). Of the 9 cases of tumor reduction, 5 cases (55.6%) continued to experience reduction. The change in tumor size and the change in tumor stain were not necessarily consistent at 2 weeks. In the patient who received a lenvatinib starting dose of 4 mg/day, the maximum tumor size decreased after the lenvatinib dose was increased, parallel to the change in tumor stain.

Tumor markers change after lenvatinib treatment in responders and non-responders.

Changes in AFP and DCP levels during lenvatinib administration are illustrated in Figure 5. The AFP level was decreased 2 weeks after the start of treatment in 11 cases, and the decrease continued in 8 of these cases (72.7%). In 2 cases, the AFP level increased 2 weeks after the start of treatment, and the increase continued in 1 of these cases (50%). No significant difference was observed between the responders group and the non-responders group in change of AFP value at 2 weeks after treatment. Similarly, no significant difference was observed between the responder group and the non-responder group in the change in DCP value two weeks after the treatment.

Comparison of responder and non-responder characteristics at baseline and at 2 weeks after treatment initiation

The background characteristics of responders and non-responders at 12 weeks were compared between baseline and 2 weeks after treatment initiation (Table 3). No significant differences between responders and non-responders were observed at baseline. Furthermore, no

significant differences in many characteristics were observed between groups 2 weeks after treatment initiation. A rate of change in tumor stain <0.8 at 2 weeks after treatment was a significantly predictive factor of a 12-week response in advanced HCC. However, significant differences in the presence or absence of a lenvatinib dosing suspension period and in the presence or absence of the dose reduction from the maximum value during the first 2 weeks were found between groups.

Discussion

Single-agent therapy has been used in HCC since the introduction of sorafenib in 2009. In 2017, regorafenib was approved as a second-line treatment, and in 2018, lenvatinib was approved as a first-line treatment. Lenvatinib is a molecularly-targeted agent developed in Japan. It was initially indicated for unresectable thyroid cancer in 2015; the indication was expanded to include unresectable HCC in March 2018. Lenvatinib is an oral multikinase inhibitor that inhibits vascular endothelial growth factor (VEGF) receptors 1-3 (VEGFR 1-3), fibroblast growth factor (FGF) receptors 1-4 (FGFR1-4), platelet-derived growth factor (PDGF) receptor α (PDGFRA), stem cell factor receptor (KIT), and rearranged during transfection receptor (RET) [6,7]. Dual inhibition of the VEGF and FGF pathways in endothelial and tumor cells results in the concomitant suppression of activity of factors involved in both angiogenesis and tumor growth.

In a Phase 2 trial of lenvatinib 12 mg/day in patients with Child-Pugh A disease, the response rate was 37%. However, 50% of patients required lenvatinib dose reduction or withdrawal due to AEs [8]. Lenvatinib was compared to sorafenib as a first-line treatment for unresectable HCC in the multicenter, randomized (1:1 ratio), open-label, non-inferiority REFLECT Phase III trial. Overall survival of patients who received lenvatinib was shown to be non-inferior to that associated with sorafenib in patients with untreated advanced HCC [4]. With respect to real-world clinical practice data in Japan, one study reported a ORR and DCR of 38.5% and 80.8%, respectively at 4 weeks, and 32.4% and 70.3%, respectively, at 12 weeks (n=37) [9]. In the present study, the ORR and DCR at 2 weeks were 53% and 87%, respectively, and 73% and 73%, respectively, at 12 weeks. Lenvatinib therefore appears to have very high therapeutic efficacy in HCC. However, many AEs can lead to discontinuation and dose reduction of lenvatinib [4,8], which may worsen patient performance status (PS). Therefore, to determine appropriate dosing of lenvatinib, early discontinuation, early dose reduction, and early prediction of treatment efficacy are considered to be necessary. AEs occurred during the

observation period in all 15 of the present patients, although the types and grades of AEs differed between patients. Understanding the benefit of lenvatinib early during treatment might thus be necessary to avoid unintended AEs.

In this study, mRECIST was used to determine treatment efficacy at 12 weeks. In HCC, many recent studies have shown a poor correlation between the clinical benefit provided by TKIs such as sorafenib or by locoregional interventional therapies using conventional methods of response assessment. Anatomic tumor response metrics can be misleading when applied to molecularly-targeted therapies or locoregional therapies in HCC. Therefore, mRECIST is often used to determine the therapeutic efficacy of HCC [10]. However, it is unclear whether observed tumor stain reductions are directly related to tumor cell necrosis. Therefore, in the present study, we evaluated not only the tumor shrinkage rate but also the tumor stain reduction rate on imaging at 2 weeks.

In the present study, although the degree of change in tumor stain at 2 weeks varied, a decreased tumor stain was observed in many cases. Thus, these results suggest that lenvatinib has a reducing effect on early tumor stain.

The results of this study also showed that it is possible to objectively assess treatment efficacy using CT very early (2 weeks) after treatment initiation, which can help in the determination of whether treatment should be continued. Changes in arterial blood flow after 2 weeks were evaluated by comparing CT values in the tumor by CE-CT examination so as to be an objective evaluation.

In cases in which the tumor stain decreased at 2 weeks, a therapeutic effect could be obtained at 12 weeks by continuing lenvatinib treatment with sufficient side effect management. In addition, we consider that prevention of PS decline can lead to second-line treatment of HCC.

At the 12-week treatment evaluation, in which responders and non-responders were compared, significant differences were observed between the two groups with respect to the presence or absence of dose reduction and lenvatinib discontinuation. Thus, maintaining the

lenvatinib dose and continuing treatment is important for lenvatinib efficacy.

Lenvatinib has been approved for about 1 year, yet few reports of real-world clinical data have been published. Kodama et al. showed that the AFP value after 2 weeks is useful for predicting the subsequent treatment effect [11]; however, AFP was not a predictor in the present study. The reason for this difference is likely due to the higher AFP values in the study of Kodama et al. Therefore, for lenvatinib treatment of HCC patients with low AFP, blood flow reduction at 2 weeks after initial treatment may be a predictor of therapeutic efficacy. Furthermore, no studies have evaluated tumor stain or tumor size using CT as early as 2 weeks after treatment initiation. Therefore, the results of this study may be very important to optimize future lenvatinib treatment.

This study has some limitations. First, the number of cases was very small. In the future, it is necessary to accumulate data from a large number of cases from real clinical practice. Second, the observation period was very short. Therefore, comparison of the overall survival observed in this analysis to that observed in other studies is difficult at present; the only endpoint in this study was treatment efficacy on target nodules. The third limitation is that all of the present cases had HCCs characterized by a high tumor stain. Tumor stain changes with tumor differentiation in HCC, so many tumors in which the stain of HCC is reduced are observed in clinical practice. Therefore, the results of this study do not clarify the antitumor efficacy of lenvatinib in patients with the latter type of HCC.

In conclusion, reduction in tumor stain 2 weeks after lenvatinib treatment may be an early biomarker of efficacy at 12 weeks in patients with unresectable HCC.

Acknowledgments

The authors express their gratitude for the valuable support of Ms. Miwako Hoshino, Ms. Yuka Sato, Ms. Tomoko Nagaura, Ms. Yuki Nozaki, Ms. Chikako Nishi, Ms. Atsuko Ishibashi, Ms.

Eri Yamauchi, and Ms. Motoko Kawashima from the Laboratory at the Department of Gastroenterology, Faculty of Medicine, Fukuoka University.

Statement of Ethics

This study was conducted in accordance with the Declaration of Helsinki, and the study protocol was approved by the ethics committee of our hospital (Approval number; U20-05-004). Written informed consent was obtained from each participating patient.

Competing Interests

The authors have no competing interests to declare.

Disclosure Statement

The authors declare no conflicts of interest.

Funding Sources

The authors have no funding sources to declare.

Author Contributions

Satoshi Shakado contributed to analysis and interpretation of data, and assisted in the preparation of the manuscript. All other authors have contributed to data collection and interpretation, and critically reviewed the manuscript. All authors approved the final version of the manuscript, and agree to be 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.

References

1. WHO, International Agency for Research on Cancer, GLOBOCAN 2012.
2. Asayama Y, Yoshimitsu K, Nishihara Y, Irie H, Aishima S, Taketomi A, Honda H. Arterial blood supply of hepatocellular carcinoma and histologic grading: radiologic-pathologic correlation. AJR Am J Roentgenol. 2008 Jan;190(1): W28-34.
3. Lencioni R, Josep M, Llovet JM. Modified RECIST (mRECIST) Assessment for Hepatocellular Carcinoma. Seminars in Liver Disease 2010; 30(1):52-60.
4. Kudo M, Finn RS, Qin S, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised Phase 3 non-inferiority trial. Lancet. 2018;391(10126):1163–1173.
5. Kuzuya T, Ishigami M, Ishizu Y, et al. Early Clinical Response after 2 Weeks of Sorafenib Therapy Predicts Outcomes and Anti-Tumor Response in Patients with Advanced Hepatocellular Carcinoma. PLoS One. 2015 Sep 30;10(9).
6. Matsui J, Funahashi Y, Uenaka T, Watanabe T, Tsuruoka A, Asada M. Multi-kinase inhibitor E7080 suppresses lymph node and lung metastases of human mammary breast tumor MDA-MB-231 via inhibition of vascular endothelial growth factor-receptor (VEGF-R) 2 and VEGF-R3 kinase. Clin Cancer Res. 2008 Sep 1;14(17):5459-65.
7. Yamamoto Y, Matsui J, Matsushima T, Obaishi H, Miyazaki K, Nakamura K, Tohyama O, Semba T, Yamaguchi A, Hoshi SS, Mimura F, Haneda T, Fukuda Y, Kamata JI, Takahashi K, Matsukura M, Wakabayashi T, Asada M, Nomoto KI, Watanabe T, Dezso Z, Yoshimatsu K, Funahashi Y, Tsuruoka A. Lenvatinib, an angiogenesis inhibitor targeting VEGFR/FGFR, shows broad antitumor activity in human tumor xenograft models associated with microvessel density and pericyte coverage. Vasc Cell. 2014 Sep 6; 6: 18.
8. Ikeda K, Kudo M, Kawazoe S, et al. Phase 2 study of lenvatinib in patients with advanced hepatocellular carcinoma. J Gastroenterol. 2017;52(4):512–519.
9. Hiraoka A, Kumada T, Kariyama K, Takaguchi K, Atsukawa M, Itobayashi E, Tsuji K,

Tajiri K, Hirooka M, Shimada N, Shibata H, Ishikawa T, Ochi H, Tada T, Toyoda H, Nouso K, Tsutsui A, Itokawa N, Imai M, Joko K, Hiasa Y, Michitaka K; Real-life Practice Experts for HCC (RELPEC) Study Group, HCC 48 Group (hepatocellular carcinoma experts from 48 clinics in Japan). Clinical features of lenvatinib for unresectable hepatocellular carcinoma in real-world conditions: Multicenter analysis. Cancer Med. 2019 Jan;8(1):137-146.

10. Edeline J, Boucher E, Rolland Y, et al. Comparison of Tumor Response by Response Evaluation Criteria in Solid Tumors (RECIST) and Modified RECIST in Patients Treated with Sorafenib for Hepatocellular Carcinoma. Cancer 2011; Epub ahead of print.
11. Kodama K, Kawaoka T, Namba M, Uchikawa S, Ohya K, Morio K, Nakahara T, Murakami E, Yamauchi M, Hiramatsu A, Imamura M, Chayama K, Aikata H. Correlation between Early Tumor Marker Response and Imaging Response in Patients with Advanced Hepatocellular Carcinoma Treated with Lenvatinib. Oncology. 2019;97(2):75-81.

Figure Legends

Figure 1. Flow chart of the study design. A total of 23 patients met the inclusion criteria. Eight patients were rejected due to exclusion criteria.

Figure 2. Rate of change in tumor stain to HCC after lenvatinib treatment. The tumor stain was reduced in 13 patients 2 weeks after treatment initiation. Of the 13 patients with a decreased tumor stain at 2 weeks, the tumor stain continued to diminish in 10 patients (76.9%).

Figure 3. Changes in tumor stain at 2 weeks predict response rate at 12 weeks after treatment initiation. The responders group included patients with PR at 12 weeks, while the non-responders group included patients with PD.

Figure 4. Changes of maximum tumor diameter after lenvatinib treatment.

Figure 5. Tumor markers changes after lenvatinib treatment in responders and non-responders.

Figure 1.

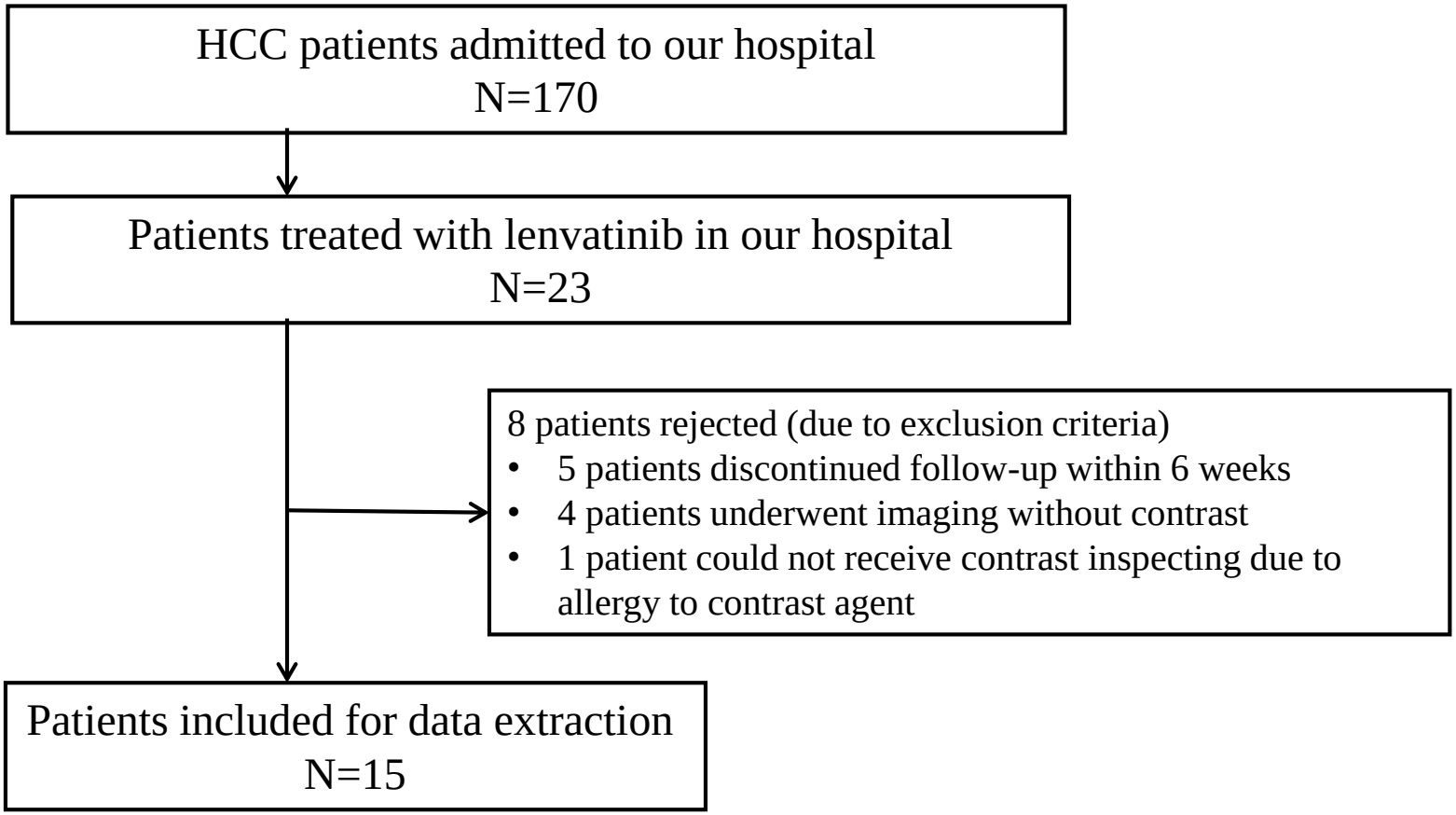
HCC patients admitted to our hospital
N=170
Patients treated with lenvatinib in our hospital
N=23
8 patients rejected (due to exclusion criteria)
• 5 patients discontinued follow-up within 6 weeks
• 4 patients underwent imaging without contrast
• 1 patient could not receive contrast inspecting due to allergy to contrast agent
Patients included for data extraction
N=15

Table 1. Baseline characteristics.

	N=15
Age, years (range)	71 (55-85)
Gender, male/female	13/2
Body weight, kg (range)	55.4 (43.5-69.8)
Etiology, HBV/HCV/NBNC	0/6/9
ECOG PS, 0/1	10/5
Prior TKI treatment, no/yes	12/3
Child-Pugh score, 5/6/7	8/5/2
BCLC stage, A/B/C	0/4/11
Tumor diameter, mm (range)	34 (14-200)
Tumor fibrous capsule, present/absent	7/8
Extrahepatic metastasis, present/absent	6/9
Vascular invasion, present/absent	9/6
Liver fibrosis, CH/LC	6/9
AFP, μg/L (range)	42.8 (4.0-74,680.5)
DCP, AU/L (range)	1,017 (13-516,327)
Observation period, days (range)	190 (83-330)

HBV, hepatitis B virus; HCV, hepatitis C virus; NBNC, non-HBV and non-HCV; ECOG, Eastern Cooperative Oncology Group; PS, performance status; TKI, tyrosine kinase inhibitor; BCLC, Barcelona Clinic Liver Cancer; CH, chronic hepatitis; LC, liver cirrhosis; AFP, alpha-fetoprotein; DCP, des-γ-carboxy prothrombin

Table 2. Time-series dosage within 8 weeks.

	Week							
	1	2	3	4	5	6	7	8
No. of cases (interruptions)	15 (0)	15 (1)	15 (1)	15 (1)	15 (1)	15 (2)	14 (3)	13 (4)
Median dose, mg/day (range)	8 (4-12)	8 (4-12)	8 (0-12)	8 (0-12)	8 (0-12)	8 (0-12)	8 (0-12)	8 (0-12)

Figure 2.

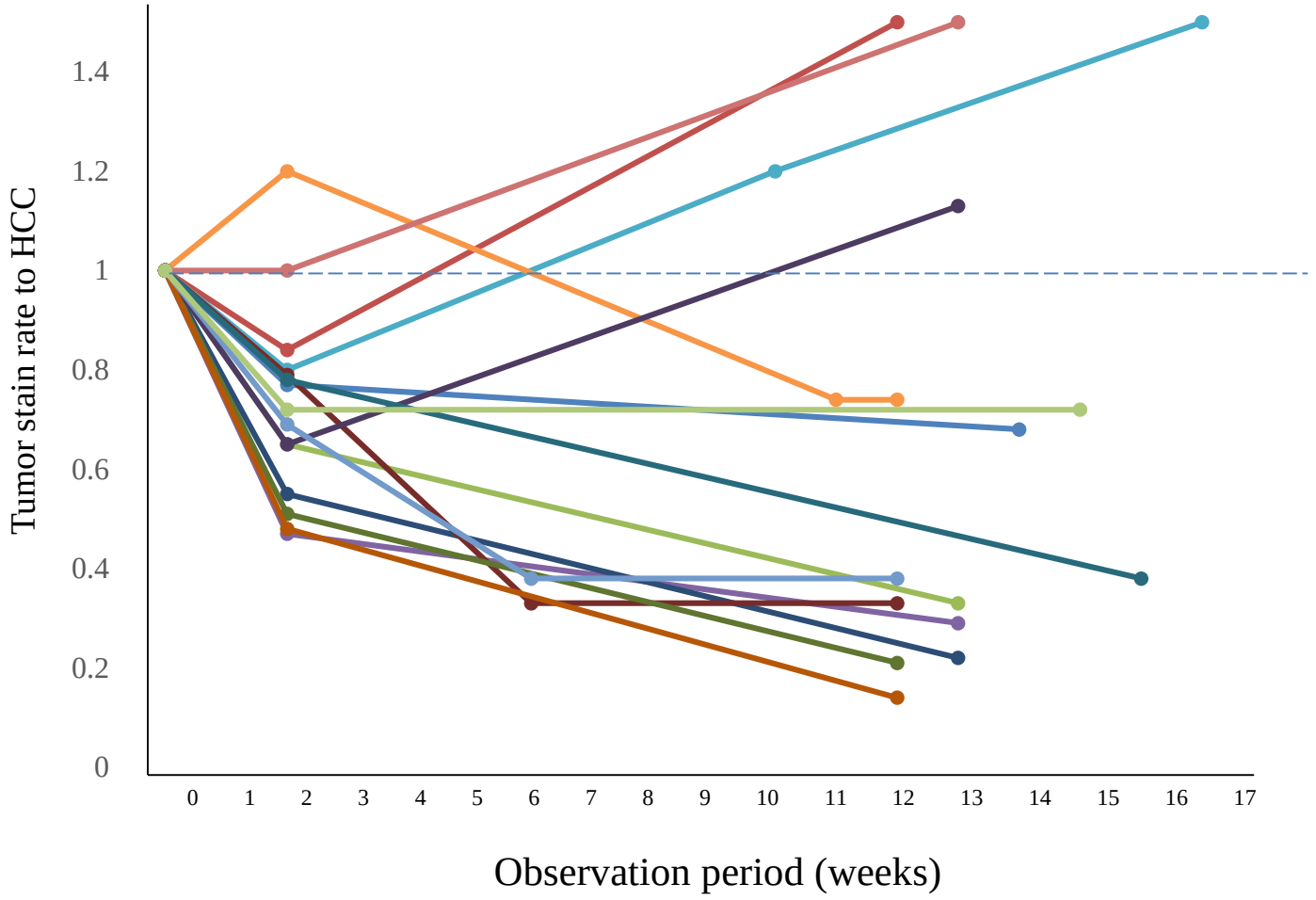
Tumor stain rate to HCC
1.4
1.2
1
0.8
0.6
0.4
0.2
0
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17
Observation period (weeks)

Figure 3.

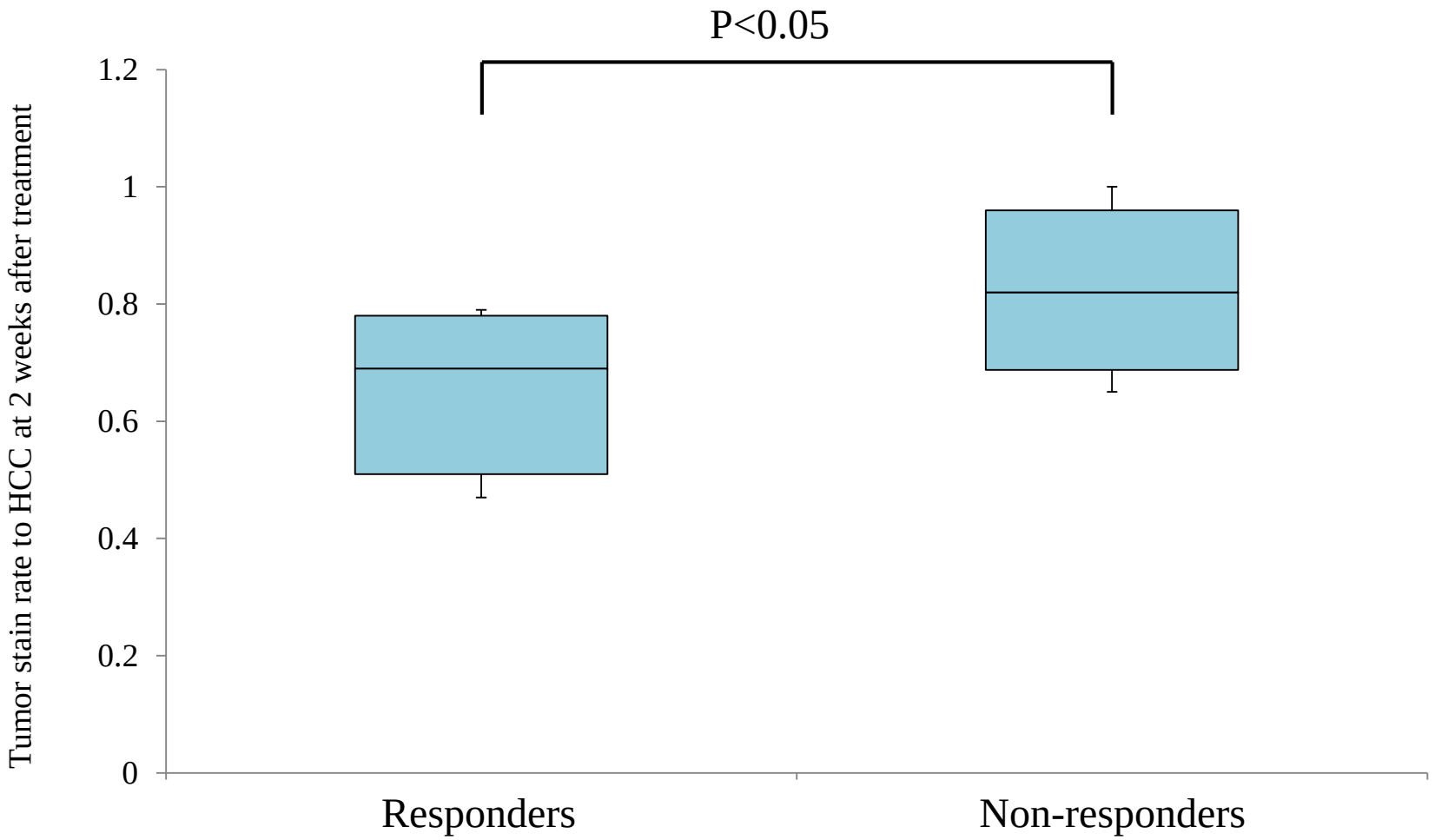
P<0.05
Tumor stain rate to HCC at 2 weeks after treatment
1.2
1
0.8
0.6
0.4
0.2
0
Responders
Non-responders

Figure 4.

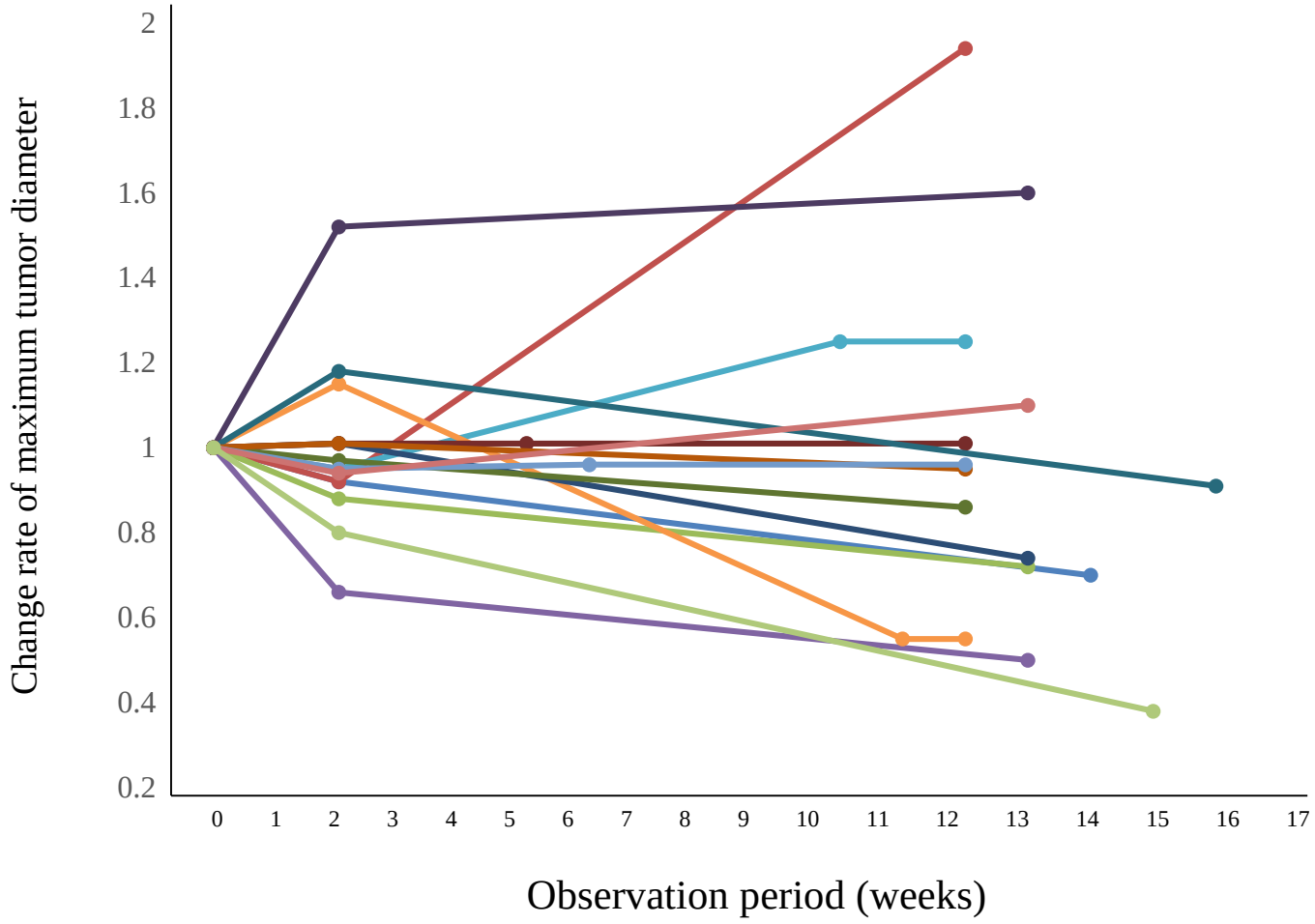
Change rate of maximum tumor diameter
2
1.8
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17
Observation period (weeks)

Figure 5.

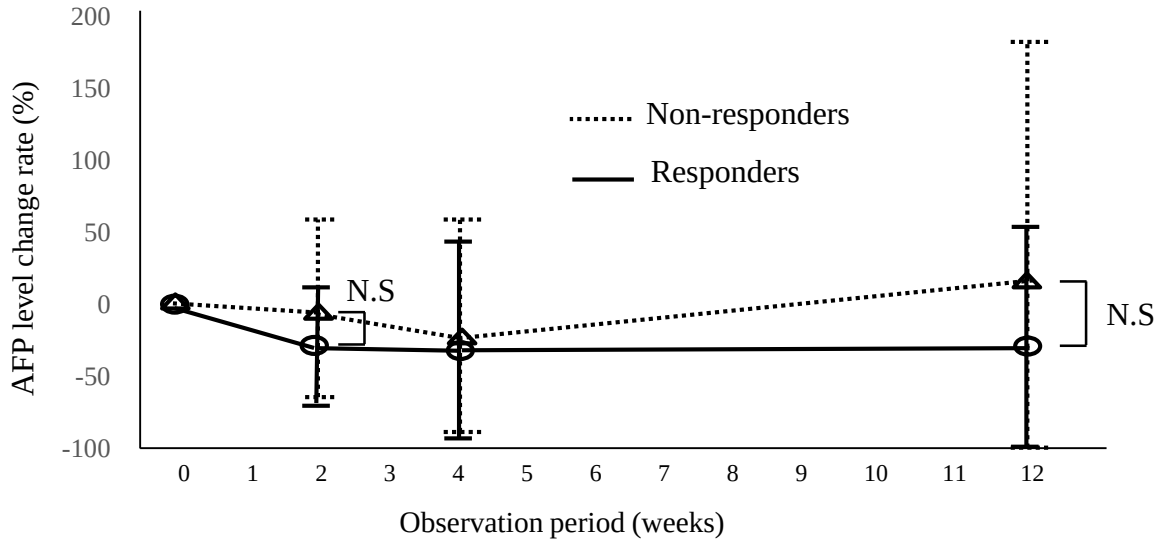
200
150
100
50
0
-50
-100
AFP level change rate (%)
Non-responders
Responders
N.S
N.S
0
1
2
3
4
5
6
7
8
9
10
11
12
Observation period (weeks)

Table 3. Characteristics of responders and non-responders at the start of treatment and after 2 weeks

	Responders (N=11)	Non-responders (N=4)	P value
At the start of treatment			
Age, years (range)	70 (55-82)	74 (64-85)	0.571
Gender, male/female	10/1	3/1	0.476
Body weight, kg (range)	55.2 (43.5-68.2)	59.7 (46.2-69.8)	0.851
Etiology, HBV/HCV/NBNC	0/4/7	0/2/2	0.634
ECOG PS, 0/1	8/3	2/2	0.560
Child-Pugh score, 5/6/7	7/3/1	1/2/1	0.385
BCLC stage, B/C	3/8	1/3	0.930
Tumor diameter, mm (range)	51 (20-200)	29 (14-69)	0.226
Tumor fibrous capsule, present/absent	5/6	2/2	0.876
Extrahepatic metastasis, present/absent	4/7	2/2	0.634
Vascular invasion, present/absent	7/4	2/2	0.634
Liver fibrosis, CH/LC	4/7	2/2	0.634
AFP, μg/L (range)	163.3 (10.2-74,680.5)	52.6 (4.2-23,869.3)	0.661
AFP-L3, % (range)	31.0 (0.5-99.5)	6.6 (0.5-60.8)	0.851
DCP, AU/L (range)	752 (53-122,625)	38,875 (222-516,327)	0.226
At 2 weeks after treatment start			
Child-Pugh score Deterioration/Improvement/Unchanged	3/0/8	1/0/3	0.930
Rate of change in tumor stain <0.8, yes/no	10/1	1/3	0.033
Change of AFP value, 2W/0W	0.83 (0.28-1.11)	0.89 (0.35-1.59)	0.661
Change of AFP-L3, 2W/0W	1.01 (0.89-1.13)	1.02 (0.94-2.16)	1.000
Change of DCP value, 2W/0W	1.17 (0.19-1.98)	1.19 (0.62-2.16)	0.949
Discontinuation, yes/no	2/9	4/0	0.011
Dose reduction, yes/no	3/8	4/0	0.026

HBV, hepatitis B virus; HCV, hepatitis C virus; NBNC, non-HBV and non-HCV; ECOG, Eastern Cooperative Oncology Group; PS, performance status; BCLC, Barcelona Clinic Liver Cancer; CH, chronic hepatitis; LC, liver cirrhosis; AFP, alpha-fetoprotein; DCP, des-γ-carboxy prothrombin; 2W, 2 weeks; 0W, 0 weeks