Efficacy of lenvatinib and transarterial chemoembolization combination therapy in patients with hepatocellular carcinoma administered an insufficient dose of early lenvatinib

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Abstract. Recently, the relationship between the relative dose intensity (RDI) and efficacy was demonstrated for lenvatinib therapy in patients with advanced hepatocellular carcinoma (HCC), with a higher RDI of lenvatinib monotherapy indicating a higher efficacy. However, not every patient can tolerate a high RDI during the course of treatment; therefore, add-on combination therapy may be necessary for patients requiring a low RDI. The addition of transarterial chemoembolization (TACE) to lenvatinib therapy improves clinical outcomes. Therefore, the aim of the present study was to compare the clinical outcomes of lenvatinib plus TACE (the LEN-TACE group) with those of lenvatinib alone (the LEN group) in patients with unresectable HCC with a high- or low-RDI. A total of 66 patients with advanced HCC were enrolled in the present retrospective study. Eligible patients were those who initiated lenvatinib monotherapy between April 2018 and September 2020. Of these patients, 29 had an 8-week RDI of ≥60%, 6 of which received LEN-TACE. A further 37 patients had an 8-week RDI of <60%, 7 of which received LEN-TACE. In the high-RDI group, both the radiological evaluations and the overall survival (OS) time were improved in those in the low-RDI group. In addition, the median OS of patients treated with LEN-TACE was longer compared with that of patients treated with lenvatinib alone in the low-RDI group (P=0.0467). Therefore, the results of the present study revealed that early TACE should be considered instead of continuing lenvatinib only treatment in patients receiving an insufficient dose of lenvatinib, such as those with an 8-week RDI of <60%.

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Introduction

Hepatocellular carcinoma (HCC) was the third most lethal cancer and the sixth most frequently diagnosed cancer globally in 2020, with an estimated 830,000 deaths and 906,000 new cases (1). The number of new liver cancer cases continues to increase and an occurrence of ≥1 million is estimated by 2025 (2).

Unresectable HCC is defined when a patient is not a candidate for resection or ablation. These patients are classified as stage B or C according to the Barcelona Clinical Liver Cancer (BCLC) staging system, updated version 2022 (3), which is widely used to classify liver cancer for treatment. Patients with BCLC stage B or intermediate stage HCC typically undergo transarterial chemoembolization (TACE) as the first choice of treatment, and patients with BCLC stage C or advanced stage HCC (for example, patients with a portal invasion or extrahepatic spread) typically undergo systemic therapies as the first choice of treatment (4).

Lenvatinib (Lenvima®; Eisai Co., Ltd.) exhibits antitumor and angiogenesis inhibitory effects on the basis of the dual inhibition of the vascular endothelial growth factor (VEGF) and fibroblast growth factor pathways (5). In a comparison of lenvatinib and sorafenib treatments, the median overall survival (OS) for lenvatinib showed a non-inferiority to sorafenib. Furthermore, lenvatinib therapy significantly prolonged the progression-free survival (PFS) time and the time to progression compared with sorafenib therapy. The objective response (OR) rates categorized by the modified Response Evaluation Criteria in Solid Tumors (mRECIST) were 24.1 vs. 9.2% for lenvatinib and sorafenib, respectively (6).

In clinical practice, patients administered lenvatinib therapy often experience dose modification due to a number of situations, including adverse events (AEs), deterioration of hepatic reserve function and a decline in Eastern Cooperation Oncology Group performance status (ECOG PS). Naturally, dose reductions diminish the therapeutic effects of the drug (7-9). The relative dose intensity (RDI) is the percentage amount out of the dose intensity delivered compared with the reference standard dose intensity for a regimen of

chemotherapy including tyrosine kinase inhibitors. Treatment with a higher RDI may enhance the treatment outcomes due to the higher plasma concentration of the drug (10). In a lenvatinib study, patients administered an 8-week RDI of ≥75% had significantly better response rates (68 vs. 20%) and a more prolonged PFS time compared with those administered an 8-week RDI of <75% (11).

TACE is recommended by a number of clinical practice guidelines worldwide for patients with intermediate-stage HCC: American Association for the Study of Liver Disease (AASLD), European Association for the Study of the Liver (EASL), Japan Society of Hepatology (JSH) (4,12,13). Based on randomized controlled trials comparing the prognosis of patients with multiple HCCs treated with TACE or symptomatic therapy, TACE has been recommended as the treatment of choice for these patients (14). High tumor recurrence rates are commonly found in clinical practice; thus, this treatment is typically repeated a number of times and may cause a decline in the hepatic reserve, leading to poor patient prognoses (15). Pre-treatment with sorafenib prior to TACE has been shown to result in a significantly longer interval between procedures, resulting in less hepatic deterioration (16). TACE increases tumor hypoxia, which activates hypoxic inducible factor-1α, promotes the upregulated expression of proangiogenic factors, such as VEGF and platelet-derived growth factor, and results in the promotion of tumor angiogenesis (17-19). The addition of antiangiogenic medication to TACE may reduce tumor size and vascular density; thus, this treatment may prolong the survival time compared with using TACE alone (20). According to the results of the LAUNCH trial, which was a randomized clinical trial, the addition of lenvatinib to TACE (LEN-TACE) exhibited an improved coordinated antitumor effect, and thus LEN-TACE had improved clinical outcomes compared with lenvatinib treatment alone in patients with advanced HCC. The results revealed a statistically significant improvement in the median PFS time in the LEN-TACE group compared with the lenvatinib alone (LEN) group (10.6 vs. 6.4 months, respectively), and a higher OR rate according to mRECIST (54.1 vs. 25.0%, respectively) (21).

To date and to the best of our knowledge, there have been no reports examining how the efficacy of a combination of lenvatinib with TACE varies with the RDI of lenvatinib. Therefore, the present study examined whether there is a difference in the combined effect of TACE with a high or low 8-week RDI of lenvatinib.

Materials and methods

Patient characteristics. The present study retrospectively reviewed the medical records of 66 patients with unresectable HCC who were treated with lenvatinib at Kansai Medical University (Hirakata, Japan). Patients were included if they were aged ≥20 years, diagnosed with unresectable HCC or BCLC stage B or C, had a Child-Pugh grade A or B, and had no prior history of treatment with lenvatinib. Patients were excluded if they had decompensated liver function or poor hepatic reserve, a history of other previous or current advanced cancers as comorbidities, a short of observation period (<8 weeks), incomplete medical records or missing data, an inability to undergo imaging with contrast media, lenvatinib therapy combined with treatments other than TACE. Eligible patients were those who initiated lenvatinib therapy between April 2018 and September 2020. Among these patients, the etiology was considered to be hepatitis B virus (HBV) if the test for the HBV surface antigen was positive, the etiology was considered to be hepatitis C virus (HCV) if the test for anti-HCV antibodies was positive and the etiology was considered to be non-B-non-C (NBNC) hepatitis if the tests for both HBV surface antigen and HCV antibodies were negative. To access hepatic reserves, the Child-Pugh and modified albumin-bilirubin (ALBI) grades were determined as previously reported (22-24). HCC was diagnosed using contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) (4,12,13). For atypical imaging results, histopathology was performed to confirm the diagnosis.

Treatment protocol and RDI. Lenvatinib was orally administered to patients with unresectable HCC, and both the body weight and hepatic reserves of the patient were considered for determining the dosage of lenvatinib. Lenvatinib was administered at a starting dose of 8 or 12 mg once daily for those ≤60 kg or >60 kg, respectively (25). The starting dose was 8 mg for patients with Child-Pugh grade B. Dose reduction was administered at the consideration of the attending physician based on the recent guideline of dosage modification for patients with drug-related toxicities (26). Unacceptable toxicity, grade ≥3 according to the Common Terminology Criteria for AEs (CTCAE) (27) definition, or the progression of disease were considered for the discontinuation of lenvatinib. The RDI was determined as previously reported (10,11,28), by dividing the dose delivered by the reference dose of the regimen. Combined immunotherapy is a standard treatment for unresectable HCC (4). In Japan, combined immunotherapy was approved in 2020; therefore, for patients who received treatment before that period were treated with lenvatinib or sorafenib as the first-line therapies. In the present study, there were 17 (58.6%) and 29 (78.3%) patients who received lenvatinib as a first-line therapy in the high- and low-RDI groups, respectively. Furthermore, there were 12 (41.3%) and 8 (21.6%) patients who received sorafenib as a first-line therapy and then switched to lenvatinib in the high- and low-RDI groups, respectively. However, only data from the period during lenvatinib therapy were analysed in the present study. After discontinuation of lenvatinib therapy, several treatments were continued as second- and third-line treatments, with combined immunotherapy being the main post-lenvatinib treatment for 8 (27.6%) and 7 (18.9%) patients in the high- and low-RDI groups, respectively (Table SI). After starting lenvatinib treatment, the attending physician considered the suitability of performing TACE based on the imaging evaluations of each patient. The median timing of TACE after lenvatinib treatment was 180.5 days (range, 64-365) among 6 patients in the high-RDI group and 38 days (range, 6-512) in 7 patients in the low-RDI group (P=0.1741). A total of three variations of TACE procedures were used based on the chemotherapy administered: Conventional (c)TACE, which uses an epirubicin (Kyowa Hakko Bio Co., Ltd.)-lipiodol (Guerbet Japan Co., Ltd.) suspension; the IA-call® procedure, which uses a cisplatin fine powder formulation (IA-call®; Nippon Kayaku, Co., Ltd.); and drug-eluting beads (DEB)-TACE, which uses epirubicin accompanied by DEBs (DC bead™,

Boston Scientific Corporation). After the cytotoxic agents were completely intra-arterially injected, an embolic agent, gelatin sponge particles (Gelpart®; Nippon Kayaku Co., Ltd), was administered until the complete cessation of blood supply to the nodules. The details of each patient are presented in Table SII. Administration of lenvatinib was discontinued for a minimum of 2 days prior and after TACE. Lenvatinib was then readministered at the same dose as previously given before discontinuation, after determining that the status and liver biochemical results of the patient were adequate.

Evaluation criteria for AEs and treatment response. The CTCAE (version 5.0) was applied to assess any AEs (27). The outcome of the treatment response was evaluated according to the RECIST 1.1 and mRECIST guidelines using CT or MRI with the triphasic scanning technique (29,30). Tumors were evaluated once within 8 weeks of lenvatinib initiation and then every 8-12 weeks thereafter. In addition, for patients who had additional TACE treatment, imaging evaluations were performed within 4 weeks following TACE.

Statistical analysis. Continuous variables are presented as the median (range) and as n (%) for categorical variables. Between-group comparisons of continuous variables were analyzed using the Mann-Whitney U test, and between-group comparisons of categorical variables were analyzed using Fisher's exact test or the χ^2 test (if the criteria were matched). Changes in liver function before and after lenvatinib treatment in each group were analyzed using the Wilcoxon signed-rank test. Kaplan-Meier analysis was used to estimate the OS, which were analyzed using the log-rank test. $P<0.05$ was considered to indicate a statistically significant difference.

Results

Patient characteristics. A total of 66 patients with advanced HCC were included in the present study, the baseline characteristics of which are shown in Table I. The median age of the patients was 72.5 years (range, 28-89 years) and 83.3% of the patients were male. In addition, the median body weight of the patients was 60.3 kg (range, 34-104 kg). The etiology of liver disease was classified as NBNC hepatitis (40.9%), HBV hepatitis (31.8%) or HCV hepatitis (16.7%), and HBV and HCV co-infection (10.6%). According to the hepatic reserve function, the median albumin level was 3.4 g/dl (range, 2.1-4.5 g/dl), the median total bilirubin level was 0.9 g/dl (range, 0.4-3.2 g/dl) and the median prothrombin time (PT) was 85.5% (range, 28.6-114.2%). With regards to the tumor markers, the median α-fetoprotein (AFP) level was 14.0 ng/ml (range, 2-530,000 ng/ml), and the median des-γ-carboxyprothrombin (DCP) level was 84.0 mAU/ml (range, 11-300,000 mAU/ml). Among the 66 patients, 19 had ascites (28.8%), 20 were classified as Child-Pugh grade B (30.3%), 40 were classified as ALBI grade 2b (60.6%), 45 were classified as BCLC stage B (68.2%), 11 had macroscopic portal vein invasion (16.7%) and 14 had extrahepatic spread (21.2%).

AEs associated with lenvatinib therapy in the high- and low-RDI groups. The AEs associated with lenvatinib therapy are presented in Table SIII. In the 8-week RDI ≥60% group, 65.5 and 20.7% of patients had any-grade and grade ≥3 AEs, respectively. The incidences of any AE grade of fatigue, thrombocytopenia, hand-foot-skin reaction, elevated aspartate aminotransferase, diarrhea, hypertension, proteinuria, and hyperbilirubinemia during the observation period were 34.5, 20.7, 10.3, 6.9, 10.3, 6.9, 3.4 and 3.4%, respectively. Of the grade ≥3 AEs, fatigue was observed frequently in this group of patients. Furthermore, in the 8-week RDI <60% group, 78.4 and 35.1% of patients had any-grade and grade ≥3 AEs, respectively. The incidences of any AE grade of fatigue, thrombocytopenia, hand-foot-skin reaction, elevated aspartate aminotransferase, diarrhea, decrease appetite, hypertension, proteinuria, and hyperbilirubinemia during the observation period were 37.8, 16.2, 16.2, 13.5, 2.7, 10.8, 5.4, 8.1 and 8.1%, respectively. Of the grade ≥3 AEs, elevated aspartate aminotransferase was observed frequently in this group of patients. Of the 66 included patients, 56 (84.8%) had dose reductions of

Table I. Patient baseline characteristics.

Baseline characteristics	Value
Demographic data	
Median age, years (range)	72.5 (28-89)
Male sex, n (%)	55 (83.3)
Median weight, kg (range)	60.3 (34-104)
Clinical characteristics, n (%)	
Etiology	
HBV	21 (31.8)
HCV	11 (16.7)
HBV and HCV	7 (10.6)
NBNC	27 (40.9)
Ascites	19 (28.8)
Child-Pugh	
A	46 (69.7)
B	20 (30.3)
ALBI grade	
1	9 (13.6)
2a	17 (25.8)
2b	40 (60.6)
BCLC stage	
B	45 (68.2)
C	21 (31.8)
Macrovascular invasion	11 (16.7)
Extrahepatic spread	14 (21.2)
Biochemical characteristics	
Median albumin, g/dl (range)	3.4 (2.1-4.5)
Median total bilirubin, g/dl (range)	0.9 (0.4-3.2)
Median prothrombin time, % (range)	85.5 (28.6-114.2)
Median AFP, ng/ml (range)	14.0 (2-530,000)
Median DCP, mAU/ml (range)	84.0 (11-300,000)

HBV, hepatitis B virus; HCV, hepatitis C virus; ALBI, albumin-bilirubin; BCLC, Barcelona Clinical Liver Cancer; AFP, α-fetoprotein; DCP, des-γ-carboxyprothrombin; NBNC, non-B/non-C hepatitis.

Table II. Patient background comparison of the 8-week RDI ≥60% and <60% groups.

Baseline characteristics	RDI <60% (n=37)	RDI ≥60% (n=29)	P-value
Demographic data			
Median age, years (range)	73 (28-87)	71 (36-89)	0.9639
Male sex, n (%)	29 (78.4)	26 (89.7)	0.3255
Median weight, kg (range)	61.0 (34.0-104.0)	57.2 (48.6-95.0)	0.4894
Clinical characteristics, n (%)			
Etiology			0.3853
HBV	11 (29.7)	10 (34.5)	
HCV	7 (18.9)	4 (13.8)	
HBV and HCV	2 (5.4)	5 (17.2)	
NBNC	17 (46.0)	10 (34.5)	
Ascites	13 (35.1)	6 (20.7)	0.2752
Child-Pugh			0.1797
A	23 (62.2)	23 (79.3)	
B	14 (37.8)	6 (20.7)	
ALBI grade			0.0031
1	2 (5.4)	7 (24.2)	
2a	6 (16.2)	11 (37.9)	
2b	29 (78.4)	11 (37.9)	
BCLC stage			0.9037
B	25 (67.6)	20 (69.0)	
C	12 (32.4)	9 (31.0)	
Macrovascular invasion	5 (13.5)	6 (20.7)	0.5153
Extrahepatic spread	9 (24.3)	5 (17.2)	0.5555
Biochemical characteristics			
Median albumin, g/dl (range)	3.3 (2.1-4.5)	3.7 (2.8-4.5)	0.0100
Median total bilirubin, g/dl (range)	1.1 (0.4-3.2)	0.8 (0.4-1.6)	0.0108
Median prothrombin time, % (range)	85.4 (28.6-114.2)	85.7 (62.3-110.6)	0.4156
Median AFP, ng/ml (range)	16.7 (2-530,000)	6.4 (2-1,757)	0.0346
Median DCP, mAU/ml (range)	185 (12-300,000)	43 (11-10,184)	0.0881

RDI, relative dose intensity; HBV, hepatitis B virus; HCV, hepatitis C virus; ALBI, albumin-bilirubin; BCLC, Barcelona Clinical Liver Cancer; AFP, α-fetoprotein; DCP, des-γ-carboxyprothrombin; NBNC, non-B/non-C hepatitis.

lenvatinib or were withdrawn from lenvatinib therapy due to encountering AEs.

A high RDI of lenvatinib over an 8-week period is associated with a favorable radiological response and a prolonged OS. The median RDI at 8 weeks when including all 66 patients was 55.3%. Among the 66 patients, 29 had an RDI of ≥60% for the first 8 weeks and were designated the high-RDI (RDI ≥60%) group, and 37 had an RDI of <60% for the first 8 weeks and were designated the low-RDI (RDI <60%) group. Table II shows a comparison of the patient backgrounds of these two groups of patients. There were statistically significant differences in the albumin level (P=0.0100), total bilirubin level (P=0.0108), AFP level (P=0.0346) and ALBI grade (P=0.0031) between the two groups.

The best tumor responses following treatment in the low and high 8-week RDI groups according to the RECIST and mRECIST guidelines were compared, as shown in Table III. According to the RECIST guidelines, 34.5 and 18.9% of patients in the high- and low-RDI groups had an OR rate, respectively, which was not statistically significant (P=0.1691). In the high-RDI group, the patients had a higher disease control rate compared with the low-RDI group, which was statistically significant (62.1 vs. 35.1%, respectively; P=0.0464). According to the mRECIST guidelines, 65.5 and 27.0% of the patients in the high- and low-RDI groups had an OR rate, respectively, and the difference was statistically significant (P=0.0026). In the high-RDI group, the patients had a higher disease control rate compared with the low-RDI group, which was statistically significant (69.0 vs. 43.2%, respectively; P=0.0482).

Comparison of liver function and tumor markers before and after lenvatinib administration. When comparing liver function markers before and after 8 weeks of lenvatinib treatment among patients in the high-RDI group, no significant changes were found in the albumin level, total bilirubin level, PT, DCP level, Child-Pugh score or ALBI score, but a significantly decreased AFP level was observed (P=0.0090; Table SIVA).

Table III. Comparison of the best tumor responses following treatment in the 8-week RDI ≥60% (n=29) and <60% (n=37) groups.

	RECIST			mRECIST		
Variable	RDI <60%, n (%)	RDI ≥60%, n (%)	P-value	RDI <60%, n (%)	RDI ≥60%, n (%)	P-value
Objective response	7 (18.9)	10 (34.5)	0.1691	10 (27.0)	19 (65.5)	0.0026
Complete response	2 (5.4)	4 (13.8)	0.3924	2 (5.4)	8 (27.6)	0.0171
Partial response	5 (13.5)	6 (20.7)	0.5153	8 (21.6)	11 (37.9)	0.1774
Stable disease	6 (16.2)	8 (27.6)	0.3647	6 (16.2)	1 (3.5)	0.1244
Disease control rate	13 (35.1)	18 (62.1)	0.0464	16 (43.2)	20 (69.0)	0.0482
Progressive disease	16 (43.2)	8 (27.6)	0.2097	13 (35.1)	6 (20.7)	0.2752
No evaluation	8 (21.6)	3 (10.3)	0.3225	8 (21.6)	3 (10.4)	0.3225

RDI, relative dose intensity; RECIST, Response Evaluation Criteria in Solid Tumors; mRECIST, modified RECIST.

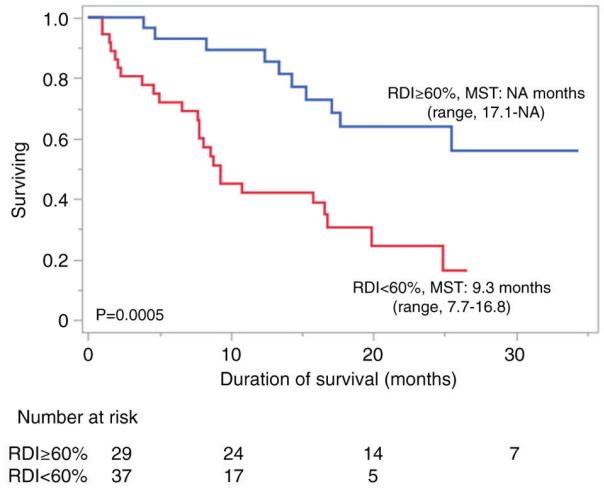

Figure 1. Comparison of the overall survival times of the high- and low-RDI groups using Kaplan-Meier analysis. RDI, relative dose intensity; MST, median survival time; NA, not applicable.

In the low-RDI group, there were no significant changes in the AFP and DCP levels, but the albumin level was significantly decreased (P=0.0023; Table SIVB). These results suggested that in the high-RDI group, 8 weeks of lenvatinib treatment provided an antitumor effect demonstrated by the significant decline in AFP level, no deterioration of hepatic reserves and more specifically, no significant decrease in albumin levels. However, in the low-RDI group, 8 weeks of lenvatinib therapy resulted in a decrease in albumin level with an inadequate antitumor effect, which was demonstrated by no significant change in the levels of both tumor markers.

A median OS time of 16.8 months (range, 10.8-25.5 months) was observed for all patients. The high-RDI group had an OS time of ≥17.1 months [range, 17.1 - not applicable (NA) months], which was significantly longer than the OS time of the low-RDI group (9.3 months; range, 7.7-16.8 months) (P=0.0005; Fig. 1).

Effect of TACE on the radiological response and OS of the high- and low-RDI groups. The radiological tumor response and impairment of liver function following LEN-TACE treatment were investigated to predict the efficacy of the addition of TACE. There were 6 patients in the high-RDI group who underwent LEN-TACE treatment. As shown in Table IVA, in the high-RDI group, the addition of TACE did not have a significant antitumor effect according to evaluations using either RECIST or mRECIST. In addition, as shown in Table SVA, when comparing the changes in liver function before and after 4 weeks of TACE treatment, no significant changes in the albumin level, total bilirubin level, AFP level, DCP level, Child-Pugh score or ALBI score were observed, but a statistically significant change in PT was found (P=0.0469). These findings suggested that the addition of TACE did not show a good radiological response in the high-RDI group, although it did not decrease the hepatic reserve.

There were 7 patients in the low-RDI group who underwent LEN-TACE treatment. As shown in Table SVB, when comparing the changes in liver function before and after 4 weeks of TACE treatment, there were no significant changes in the total bilirubin level, PT, AFP level, DCP level, Child-Pugh score or ALBI score, but the change in albumin level was statistically significant (P=0.0391). The best tumor responses, as determined using the RECIST and mRECIST guidelines, in the LEN-TACE and LEN subgroups of the low-RDI group were compared, as shown in Table IVB. According to the RECIST guidelines, 14.3 and 20.0% of patients in the LEN-TACE and LEN groups had an OR, respectively, which was not significantly different (P=0.7282), and the disease control rate was 42.9 and 33.3% in the LEN-TACE and LEN groups, respectively, which was not a statistically significant difference (P=0.6780). According to the mRECIST guidelines, the OR of patients in the LEN-TACE and LEN groups was 57.1 and 20.0%, respectively, which was not significantly different (P=0.0688); however, the disease control rate was 100 and 30% in the LEN-TACE and LEN groups, respectively, which was a statistically significant difference (P=0.0011). Conversely, 43.3% of patients in the LEN group had progressive disease, whilst there were no patients with progressive disease in the LEN-TACE group, which was a statistically significant difference (P=0.0378).

In the high- and low-RDI groups, the patients were divided into two subgroups stratified by treatment, which TACE were added or not (LEN-TACE or LEN groups) and the median OS

Table IV. Comparison of the best tumor responses following LEN-TACE treatment in the 8-week RDI ≥60% (A) and <60% (B) groups.

A, 8-week RDI ≥60% group

	RECIST			mRECIST		
Variable	LEN-TACE (n=6)	LEN (n=23)	P-value	LEN-TACE (n=6)	LEN (n=23)	P-value
OR, n (%)	3 (50.0)	7 (30.4)	0.6328	5 (83.3)	14 (60.9)	0.6328
CR, n (%)	2 (33.3)	2 (8.7)	0.1798	1 (16.7)	7 (30.4)	0.6472
PR, n (%)	1 (16.7)	5 (21.7)	0.7847	4 (66.7)	7 (30.4)	0.1638
SD, n (%)	1 (16.7)	7 (30.4)	0.6472	0 (0.0)	1 (4.4)	0.6032
Disease control rate, n (%)	4 (66.7)	14 (60.9)	0.7944	5 (83.3)	15 (65.2)	0.6328
PD, n (%)	2 (33.3)	6 (26.1)	0.7236	1 (16.7)	5 (21.7)	0.7847
NE, n (%)	0 (0.0)	3 (13.0)	0.3502	0 (0.0)	3 (13.0)	0.3502

B, 8-week RDI <60% group

	RECIST			mRECIST		
Variable	LEN-TACE (n=7)	LEN, n=30	P-value	LEN-TACE (n=7)	LEN (n=30)	P-value
OR, n (%)	1 (14.3)	6 (20.0)	0.7282	4 (57.1)	6 (20.0)	0.0688
CR, n (%)	1 (14.3)	1 (3.3)	0.3468	1 (14.3)	1 (3.3)	0.3468
PR, n (%)	0 (0.0)	5 (16.7)	0.5599	3 (42.9)	5 (16.7)	0.1563
SD, n (%)	2 (28.6)	4 (13.3)	0.3155	3 (42.9)	3 (10.0)	0.0679
Disease control rate, n (%)	3 (42.9)	10 (33.3)	0.6780	7 (100.0)	9 (30.0)	0.0011
PD, n (%)	4 (57.1)	12 (40.0)	0.4373	0 (0.0)	13 (43.3)	0.0378
NE, n (%)	0 (0.0)	8 (26.7)	0.3079	0 (0.0)	8 (26.7)	0.3079

LEN, lenvatinib; LEN-TACE, LEN plus transarterial chemoembolization; RDI, relative dose intensity; RECIST, Response Evaluation Criteria in Solid Tumors; mRECIST, modified RECIST; OR, objective response; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, no evaluation.

times were investigated. In the high-RDI group, the median OS time was 17.7 months (range, 3.9-NA months) and at least 15.3 months (range, 15.3-NA) in patients with and without TACE, respectively, which was not a significant difference in OS time (P=0.2613; Fig. 2A). However, in the low-RDI group the median OS time was at least 8.8 months (range, 8.8-NA months) and 8.1 months (range, 4.6-15.8 months) in patients with and without TACE, respectively, which was a significant difference in OS time (P=0.0392; Fig. 2B).

Discussion

Randomized trials that combined lenvatinib treatment with TACE have demonstrated the add-on effects of TACE (16,21). The results of the present study demonstrated the benefits of add-on TACE in the low-RDI subgroup, which had significantly prolonged overall survival with add-on TACE compared to no additional TACE, suggesting the efficacy of subsequent TACE in patients who received an insufficient dose of lenvatinib. However, the present study also demonstrated that there were no improvements in the tumor response in the high-RDI group with or without the addition of TACE, according to imaging results and both the RECIST and mRECIST guidelines. This may explain why the OS time was not significantly prolonged with the addition of TACE in this group. Therefore, when considering TACE for patients with a high RDI, it is important to ensure that TACE results in tumor response such as a complete response (CR). Conversely, in the low-RDI group, even if a CR was not achieved with TACE, early addition of TACE was shown to improve the therapeutic effect, when compared with the continued treatment of lenvatinib alone. As previously reported, patients who were able to maintain a high RDI had improved ALBI and Child-Pugh scores (11,28,31). Therefore, in patients with a good hepatic reserve, it may be effective to continue lenvatinib treatment alone for as long as possible and to add TACE at the point where a CR can be expected. Whereas, in patients with a poor hepatic reserve, it is difficult to maintain a high RDI and therefore a different strategy is required. Specifically, the addition of TACE early after the initiation of lenvatinib followed by a continuation of lenvatinib treatment may prolong the OS time, compared with continuing lenvatinib alone, even if the dose of lenvatinib is reduced.

TACE is known to induce the expression of angiogenic factors involved in tumor metastasis by creating an ischemic environment in the tumor (17-19,32,33). Lenvatinib has a potent anti-angiogenesis effect that inhibits these angiogenic

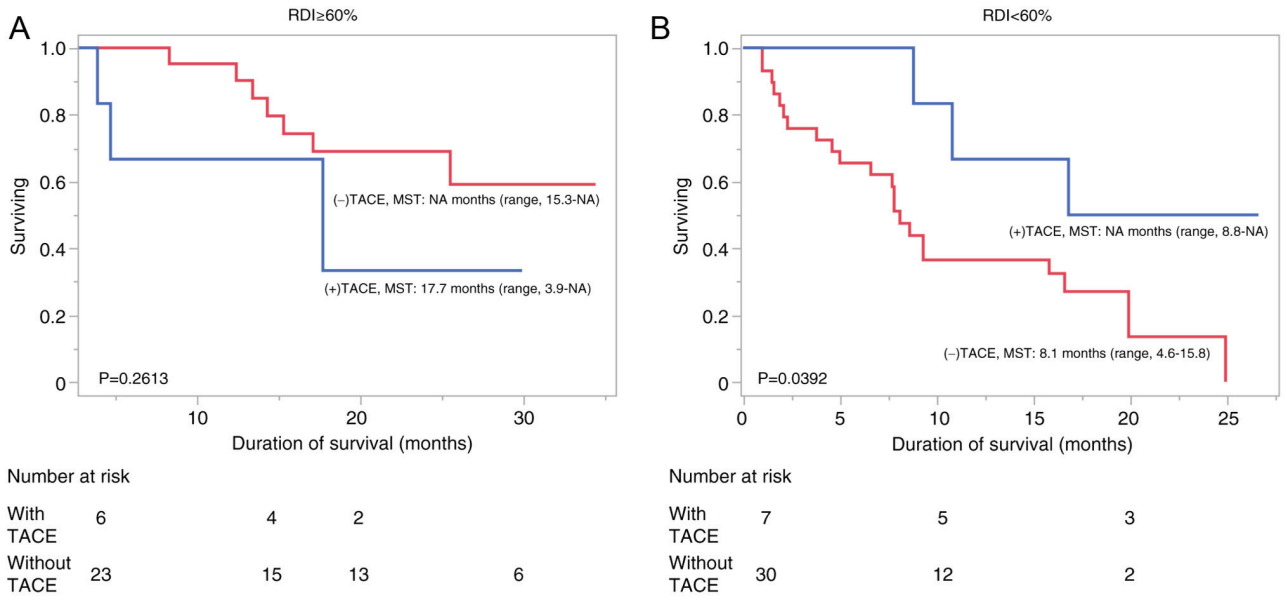

Figure 2. Comparison of the overall survival times of the with and without TACE treatment groups in the subgroup analysis. (A) Kaplan-Meier analysis demonstrating the MSTs of patients in the 8-week RDI ≥60% group (n=29). (B) Kaplan-Meier analysis demonstrating the MSTs of patients in the 8-week RDI <60% group (n=37). MST, median survival time; RDI, relative dose intensity; TACE, transarterial chemoembolization; NA, not applicable.

factors (34), thus it may suppress tumor growth after treatment with TACE (35,36). However, lenvatinib may promote tumor vascular normalization, improve embolization agent delivery, optimize the embolic effect, reduce the permeability of tumor vessel and interstitial pressure, optimize intra-tumoral delivery of systemic anticancer agents and increase response rates (37,38). The inhibitory effect of lenvatinib on angiogenesis and tumor growth after TACE may be achieved even at low doses, as was observed in the low-RDI group of the present study, which had a longer OS time after the addition of TACE. Therefore, when is the optimal time to add TACE when lenvatinib is administered to patients with impaired liver function? There are notable findings from an animal study and two clinical studies that may help answer this question. In an experiment where mice were subcutaneously implanted with mouse HCC cells, tumor vasculature was examined after only 4 days of treatment with lenvatinib or sorafenib, and lenvatinib had significantly decreased the microvascular density and normalized the tumor vasculature compared with sorafenib (39). These outcomes indicated that lenvatinib induced the normalization of HCC tumor vasculature earlier and more effectively than sorafenib, thus improving the intratumor microenvironment. In a phase Ib/II clinical study of lenvatinib therapy combined with letrozole in patients with advanced estrogen receptor^{+}/HER2^{+} breast cancer, a decrease in microvessel density and an increase in the vascular normalization index, which are surrogate markers for the VEGFR pathway, were observed in tumor tissues within 2 weeks of lenvatinib administration (40). These results indicated that the VEGFR pathway in tumor tissues was inhibited within 2 weeks of lenvatinib administration, resulting in reduced neovascularization and normalization of blood vessels through the mobilization of pericytes around leaking tumor vessels. This was demonstrated via the marked decrease in the expression of CD31^{+} in the immunohistochemistry staining results of the lenvatinib treatment group. A recently published case report regarding the short-term administration of lenvatinib in 2 patients with unresectable HCC, reported the administration of 12 mg/day for 7 days or 8 mg/day for 4 days. The results of high-resolution digital subtraction angiography after the lenvatinib treatment showed normalization of the tumor vasculature, as evidenced by the tumor staining becoming more refined and newly formed tiny tumor vessels being observed in both cases. Furthermore, perfusion 4D-CT during hepatic arteriography showed reduced arterial blood flow to the tumor after only 4 or 7 days of lenvatinib administration (41). Based on these reports, lenvatinib appears to induce a relatively early normalization of the tumor vasculature, and the addition of TACE a few days to a week after the start of lenvatinib treatment, followed by continued lenvatinib administration, appears to be an effective treatment strategy.

The present study does however have several limitations. First, this retrospective cohort study was not randomized. Second, the sample size may have been too small to detect statistically significant differences in certain treatment outcomes. Specifically, the small sample size may be why the median OS time was not significantly different between the LEN-TACE and LEN subgroups of the high-RDI group. A previous study reported that the addition of TACE to lenvatinib notably improved the CR rate and ORR compared with LEN alone in the high-RDI group (42). Likewise, the Asia-Pacific Primary Liver Cancer Expert consensus recommended superselective conventional TACE with curative intent as the first choice of treatment in the eligible patients (43). In the subgroup analysis of the high-RDI group in the present study, none of the patients who underwent TACE received superselective cTACE strategy (Table SII). This may be another reason why the results in the present study were not statistically significant. However, this preliminary report on strategies for limiting the number of patients receiving TACE according to RDI may still be useful.

In summary, consistent with previous reports, in the present study, patients who were able to maintain a high RDI of lenvatinib had an improved prognosis, and these patients also had improved ALBI and Child-Pugh scores. There was a significant difference in the radiological response and OS time with TACE combination therapy in the low-RDI group, while there was no difference in the radiological response and OS time with TACE combination therapy in the high-RDI group. From those results, we suggest that early TACE must be considered as an effective therapy, instead of continuing with lenvatinib treatment alone in patients receiving an insufficient dose of lenvatinib. Therefore, to maximize the add-on effect of TACE, an appropriate time of TACE addition should be considered for each group of patients.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

PP was responsible for the collection of data from medical records, analysis, drafting the manuscript, review and editing. TY and HK were responsible for conception and design, patient enrollment, the collection of data from medical records, analysis and drafting the manuscript. PP and TY confirmed the authenticity of all the raw data. KA, KY, HM, and KM were responsible for patient enrollment, the collection of data from medical records, analysis, review and editing of the manuscript. SS, MK, and MN were responsible for the review and editing of the manuscript, supervision and project administration. SS was responsible for conception and design. MK, and MN were responsible for patient enrollment and the collection of data from medical records. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

This study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Kansai Medical University Medical Center (Hirakata, Japan; approval no. 2022307). The requirement for informed written consent was waived due to the retrospective nature of this study. However, we maintained the opt-out policy mentioned on our hospital's webpage, whereby eligible participants were free to opt out of the study.

Patient consent for publication

Informed consent for publication was obtained in the form of an opt-out feature on our website, with the approval of the Ethics Committee of Kansai Medical University Medical Center (Hirakata, Japan).

Competing interests

The authors declare that they have no competing interests.

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