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ORIGINAL ARTICLE

# Efficacy of rechallenge transcatheter arterial chemoembolization after lenvatinib treatment for advanced hepatocellular carcinoma

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**Key words**
hepatocellular carcinoma, intolerance, lenvatinib, molecular-targeted agents, refractoriness, transcatheter arterial chemoembolization.

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**Author contribution:** Sawako Uchida-Kobayashi and Ken Kageyama were involved in conceiving the project, data analysis, and drafting the manuscript. Akira Yamamoto and Atsushi Jogo were involved in radiological assessment. Kazuhiro Matsumoto was involved in statistical assessment. Shigekazu Takemura, Naoshi Odagiri, Kohei Kotani, Ritsuzo Kozuka, Hiroyuki Motoyama, Etsushi Kawamura, Atsushi Hagihara, Hideki Fujii, Shogo Tanaka, Masaru Enomoto, and Akihiro Tamori were involved in laboratory data acquisition and clinical data analysis. Shoji Kubo, Yukio Miki, and Norifumi Kawada were involved in grand design of the study and drafting of the manuscript. All authors critically revised the report, commented on the drafts of the manuscript, and approved the final report.
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## Abstract

**Background and Aim:** We evaluated the efficacy of rechallenge transcatheter arterial chemoembolization (TACE) after lenvatinib (LEN) treatment in patients with previous TACE failure/refractoriness.
**Methods:** We enrolled 63 consecutive patients with a history of TACE failure/refractoriness prior to LEN treatment as a first-line systemic therapy. We reviewed the clinical backgrounds and courses of the patients.
**Results:** In total, 25 patients underwent rechallenge TACE after LEN due to LEN-refractoriness (17 cases) or intolerance (8 cases). A complete or partial response was obtained for 13 (65.0%) of the 20 patients whose therapeutic effects were determined. The survival rate of patients who underwent rechallenge TACE was significantly higher than that of patients who did not undergo rechallenge TACE (median survival time, not reached *vs* 403 days, $P = 0.015$). Rechallenge TACE significantly reduced the risk of death in univariate (hazard ratio [HR] 0.24, 95% confidence interval [CI] 0.08–0.69, $P = 0.008$) and multivariate analyses (HR 0.26, 95% CI 0.08–0.80, $P = 0.019$). If complete or partial response was obtained by rechallenge TACE, the median survival time of these patients was significantly longer than those of the progressive disease (PD) group ($P = 0.05$), and the median survival time of the PD group after rechallenge TACE was not different from that of the group who did not undergo rechallenge TACE ($P = 0.36$). We did not observe a decrease in the ALBI score after TACE.
**Conclusion:** Rechallenge TACE after LEN is an effective treatment that may result in a favorable prognosis.

## Introduction

Hepatocellular carcinoma (HCC) is the most common type of liver cancer and the third leading cause of cancer-related deaths worldwide.[1–3] The Barcelona Clinic Liver Cancer (BCLC) staging system is the most widely used treatment algorithm for HCC worldwide.[4–6] The prognosis of patients with early stage HCC has improved due to the development of curative therapies such as hepatectomy and radiofrequency ablation (RFA).[7–9] However, these treatments are not always administered as more than half of HCC patients are diagnosed at an advanced stage.[10] Patients with advanced HCC are usually treated with transcatheter arterial chemoembolization (TACE),[11,12] hepatic arterial infusion chemotherapy,[13] molecular-targeted agents (MTA),[7] or immunotherapy,[14] although the prognosis after treatment remains poor.

MTA therapy is the guideline-recommended global standard of care for patients with well-preserved liver function (Child–Pugh Class A) and advanced tumors, BCLC-C, or earlier stage tumors progressing to or unsuitable for locoregional therapies.[7] In Japan, lenvatinib (LEN) is the first-line MTA for HCC. LEN is an orally active tyrosine kinase inhibitor that exerts its antitumor effects by suppressing tumoral blood flow. The survival benefits of LEN were demonstrated in a Phase 3 clinical trial, the REFLECT trial, involving patients with unresectable HCC.[15] In addition, recent retrospective multicenter studies have reported the high efficacy of LEN in patients with unresectable HCC.[16,17] However, LEN is also associated with a high incidence of adverse events (AEs), which may lead to discontinuation of treatment resulting in a poor prognosis.[18] Furthermore, patients with a low relative dose intensity of LEN and poor hepatic reserve function have a poor prognosis.[19,20]

Recent research has demonstrated the effectiveness of LEN-TACE sequential treatment.[21–23] Most of the subjects in these studies were diagnosed with BCLC-B HCC, including patients who had never undergone TACE.

In clinical practice, even in patients with a history of TACE failure/refractoriness or with BCLC-C, TACE is often performed. However, it is not clear whether re-TACE (rechallenge TACE) is effective after LEN treatment for HCC in patients with a history of TACE failure/refractoriness, and whether TACE for BCLC-C HCC will improve the patient's prognosis.

In this study, we examined the efficacy of rechallenge TACE after LEN treatment for unresectable HCC in patients with a history of TACE failure/refractoriness before LEN.

## Materials and methods

This was a retrospective single-center study that enrolled consecutive patients who were administered LEN for unresectable HCCs between April 2018 and November 2020 at Osaka Metropolitan University Hospital. The diagnostic criteria for HCC, which have been described previously,[8] include hyperattenuation or hypoattenuation during the arterial and portal phase, respectively, as revealed by dynamic computed tomography (CT) or magnetic resonance imaging. We reviewed the patients' clinical backgrounds at the start of LEN treatment and the clinical courses of those administered LEN for HCC. We defined TACE failure/refractoriness according to the Japan Society of Hepatology-Liver Cancer Study Group of Japan criteria 2014,[24] and rechallenge TACE as a subsequent re-TACE for patients who received LEN treatment after a previous TACE failed or became refractory. This study was conducted in accordance with the guidelines of the Declaration of Helsinki. Written informed consent was obtained from all patients before treatment. The study protocol was approved by the Ethics Committee of the Osaka Metropolitan University Hospital (No. 2021–054).

***LEN treatment.*** In this study, LEN treatment was indicated for patients with whose liver function was Child–Pugh Class A or B, and advanced tumors, BCLC-C, or earlier stage tumors progressing to or unsuitable for locoregional therapies. LEN was administered orally, based on the patient's weight. Those who weighed <60 or ≥60 kg were initially administered 8 or 12 mg LEN daily, respectively. A dose reduction or interruption of LEN, depending on the patient's general condition and AEs, was permitted.

***TACE treatment.*** Digital subtraction angiography was performed under local anesthesia for visualization of the celiac and the common hepatic arteries using a 3- or 4-Fr catheter with a nonionic iodine contrast agent (iohexol, Omnipaque® 300 iodine, 300 mg I/mL; GE Healthcare, Tokyo, Japan). CT during hepatic arteriography (CTHA) and cone-beam CT (CBCT) during hepatic arteriography (CBCTHA) were performed using an interventional radiology CT system (nexaris Angio-CT, Siemens Healthcare GmbH, Forchheim, Germany) or a C-Arm dual-phase CBCT system (Artis zee BA Twin; Siemens Healthcare GmbH, Forchheim, Germany). Digital subtraction angiography, CTHA, CBCTHA, and CT during arterial portography were used to evaluate the vascular anatomy, tumor number and location, and portal vein patency. Subsequently, a 1.7- to 2.0-Fr microcatheter was inserted into the sub-subhepatic segment to locate the tumor. The microcatheter was advanced toward the tumor-feeding artery to avoid injection into the non-targeted arteries. Conventional TACE was performed using an emulsion of 20–50 mg of epirubicin (Nippon Kayaku Co., Ltd., Tokyo, Japan) or cisplatin (Nippon Kayaku Co., Ltd) with ethiodized oil (Lipiodol Ultra-Fluide, Guerbet Co., Ltd., Tokyo, Japan), respectively. The amounts of emulsion were determined based on the tumor sizes, tumor counts, and liver function. The maximum dose of Lipiodol® was 10 mL in one TACE session. The maximum doses of epirubicin and cisplatin were 50 mg each. The emulsion was infused into the feeding arteries followed by 1–2 mm gelatin sponge particles (Gelpart; Nippon Kayaku, Tokyo, Japan) to make the tumor stains disappear.[25,26]

***Evaluation of treatment response.*** The treatment response was evaluated according to the modified Response Evaluation Criteria in Solid Tumors (mRECIST).[27] TACE efficacy was evaluated using dynamic CT after approximately 1–3 months.

***Statistical analyses.*** All data analyses were performed using SAS (version 9.4). Data are expressed as mean ± standard deviation, medians with ranges, or numbers. Baseline characteristics of the patients were analyzed using the $\chi^2$ test, Fisher's exact test, or Mann–Whitney U test. The overall survival (OS) after the

introduction of LEN was estimated using the Kaplan–Meier method, and the log-rank test was used to compare values. Univariate and multivariate analyses were conducted using the Cox proportional hazards model to identify the factors associated with OS. Adjusted variables included sex, age (<70 or ≥70 years), etiology (viral or non-viral), alpha-fetoprotein (AFP) level (<100 or ≥100 ng/mL), albumin-bilirubin (ALBI) grade (1 or 2 and 3), BCLC stage (A and B or C), and rechallenge TACE (yes or no). Changes in the ALBI scores before and after rechallenge TACE were analyzed using the Wilcoxon signed-rank test. Statistical significance was set at $P < 0.05$.

## Results

***Patient characteristics.*** We administered LEN to 115 patients with unresectable HCCs from April 2018 to November 2020. Among them, 95 consecutive patients had a history of TACE failure/refractoriness before LEN treatment. This study included 63 patients who received LEN as the first-line systemic treatment (Fig. 1). Table 1a shows the baseline characteristics of the patients at the start of LEN. The median (interquartile range [IQR]) age of the patients was 75 (67–79) years, 54 (85.7%) patients were male, and 32 (50.8%) had BCLC-C HCCs. Of the enrolled patients, 59 (93.7%) were clinically classified as Child–Pugh Class A, and the median (IQR) ALBI score was −2.25 (−2.67 to −2.01). The average number of TACE treatments was 2.5 ± 1.4 before LEN initiation, and the median (IQR) period from initial treatment to start of LEN was 2.0 (0.9–4.7) years. None of the patients had confirmed distant metastasis at the time of first TACE. The first TACE was performed for patients with HCC localized in the liver.

***Clinical course after the start of LEN treatment.*** The initiation doses of LEN were 12, 8, or 4 mg/day. There were 51 (81.0%) patients who started taking the standard dose. During the median observation period of 344 days from the initiation of LEN, 25 patients underwent rechallenge TACE. Whether rechallenge TACE should be taken was a decision between the patient and the attending physician. The reason for rechallenge TACE was LEN refractory/intolerance (17/8), and the mean period of oral administration of LEN until rechallenge TACE was 140.4 ± 104.8 days. Eight of the 25 patients continued with LEN after rechallenge TACE. Table 1a shows that the rechallenge TACE group had significantly fewer patients with BCLC-C ($P = 0.015$) and extrahepatic metastasis ($P = 0.011$) than the non-rechallenge TACE group, but there were no significant differences in other factors. In BCLC-A and B, there was no significant difference in the patient characteristics between the rechallenge TACE and the non-rechallenge TACE groups. In BCLC-C, the number of TACE before LEN was higher in the rechallenge TACE group than in the non-rechallenge TACE group, but there were no significant differences in other factors (Table 1b).

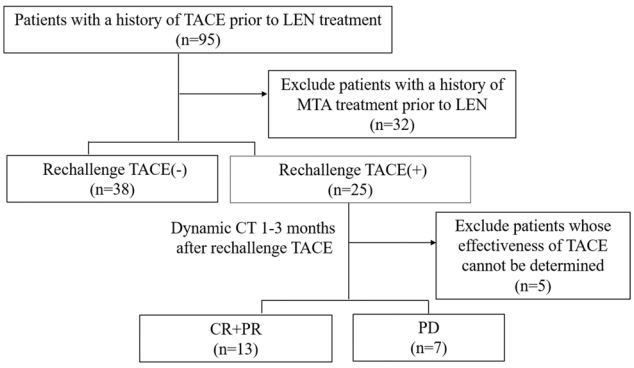


**Figure 1** Patients' clinical course. CR, complete response; CT, computed tomography; LEN, lenvatinib; PD, progressive disease; PR, partial response; TACE, transcatheter arterial chemoembolization

Figure 1 shows the patients' clinical course. Twenty patients underwent dynamic CT after 1–3 months to determine the effect of rechallenge TACE: two patients had a complete response (CR), 11 patients had a partial response (PR), and seven patients had a progressive disease (PD). Patients with CR and PR showed good Lipiodol accumulation in TACE-treated tumors. Within the observation period, 2 of the 11 patients with PR achieved CR due to RFA. Two of the CR + PR cases became cancer free, and their treatment was completed. Five PDs underwent subsequent treatment after rechallenge TACE (such as other MTAs or immune checkpoint inhibitors). Of the five patients who were not evaluated for the effect of rechallenge TACE by dynamic CT, four were evaluated by dynamic MRI, one had CR, 1 PR, and 2 PD. The remaining one started the other MTA treatment without evaluating the effect of rechallenge TACE. Of the 38 patients who did not receive rechallenge TACE, five continued LEN treatment at their request despite LEN refractory. Another 24 patients transitioned to subsequent treatment, such as other MTAs or immune checkpoint inhibitors. The remaining nine patients transitioned to best supportive care.

***Overall survival.*** The OS of the patients from the start of the LEN is shown in Figure 2a–c. Patients who underwent rechallenge TACE had a significantly longer median survival time than patients who did not undergo rechallenge TACE (not reached and 402 days, respectively, $P = 0.004$. Fig. 2a). Since it was shown that BCLC-C patients were significantly lower in the rechallenge TACE group than in the non-rechallenge TACE group (Table 1a), the OS period was analyzed separately for BLCL-AB and BCLC-C. Patients who underwent rechallenge TACE had a significantly longer median survival time than patients who did not undergo rechallenge TACE in BCLC-A or B (not reached and 527 days, respectively, $P = 0.0011$. Fig. 2b), but there was no difference in BCLC-C (439 and 402 days, respectively, $P = 0.48$. Fig. 2c). To investigate the effect of liver function, we further divided the patients into four groups: BCLC-A, B and ALBI-1, BCLC-A, B and ALBI-2, 3, BCLC-C and ALBI-1, and BCLC-C and ALBI-2, 3. In BCLC-A and B, both the ALBI-1 group and the ALBI-2, 3 groups showed significantly longer median OS time in the rechallenge TACE group than in the non-rechallenge TACE group (ALBI-1; not reached and 256 days, respectively, $P = 0.019$, Fig. S1a. ALBI-2, 3; not reached and 527 days, respectively, $P = 0.014$, Fig. S1b). On the other hand, in BCLC-C, neither ALBI-1 nor ALBI-2, 3, there was no significant difference in OS between the rechallenge TACE group and the non-rechallenge TACE group (ALBI-1; not

**Table 1** Baseline characteristics of patients with a history of TACE failure/refractoriness at the start of lenvatinib treatment

(a)

| | All patients ($n = 63$) | Rechallenge TACE (+) ($n = 25$) | Rechallenge TACE (−) ($n = 38$) | *P* value[†] |
|---|---|---|---|---|
| Median age (IQR), years | 75 (67, 79) | 76 (67, 78) | 74(67, 79) | 0.85 |
| Sex, male/female, *n* | 54/9 | 20/5 | 34/4 | 0.29 |
| Etiology, viral/nonviral, *n* | 29/34 | 11/14 | 18/20 | 0.79 |
| Child–Pugh Class A/B, *n* | 59/4 | 24/1 | 35/3 | 0.54 |
| Median ALBI score (IQR) | −2.25 (−2.67, −2.01) | −2.36 (−2.73, −2.08) | −2.24 (−2.65, −1.99) | 0.37 |
| ALBI grade 1/2a/2b/3, n | 20/11/31/1 | 8/5/12/0 | 12/6/19/1 | 0.84 |
| **BCLC stage A, B/C, *n*** | 31/32 | **17/8** | **14/24** | **0.015** |
| Vessel invasion, *n* | 14 | 4 | 10 | 0.34 |
| **Extrahepatic metastasis, *n*** | 22 | **4** | **18** | **0.011** |
| Median AFP(IQR), ng/mL | 16.1(6.2, 617.1) | 16.1 (1.9, 569.9) | 15.3 (62, 633.2) | 0.74 |
| Median PIVKA-II(IQR), mAU/mL | 139 (67, 1555) | 459(67, 579) | 177(65, 2081) | 0.40 |
| Maximal tumor size >5/≤5 cm | 44/19 | 18/7 | 26/12 | 0.76 |
| Tumor number >3/≤3 | 27/36 | 9/16 | 18/20 | 0.37 |
| Median period from initial treatment to start of LEN (IQR), years | 2.0 (0.9, 4.7) | 2.5(0.9, 4.4) | 1.8 (0.9, 6.9) | 0.94 |
| Average number of TACE treatments before LEN | 2.5 ± 1.4 | 3.0 ± 1.3 | 2.2 ± 1.4 | 0.05 |

(b)

| | BCLC-A, B | | | BCLC-C | | |
|---|---|---|---|---|---|---|
| | Rechallenge TACE (+) ($n = 17$) | Rechallenge TACE (−) ($n = 14$) | *P* value | Rechallenge TACE (+) ($n = 8$) | Rechallenge TACE (−) ($n = 24$) | *P* value |
| Median age (IQR), years | 75 (67, 78) | 75(67, 78) | 0.95 | 77 (67, 78) | 73(68, 79) | 0.78 |
| Sex, male/female, *n* | 15/2 | 12/2 | 0.83 | 7/1 | 20/4 | 0.78 |
| Etiology, viral/nonviral, *n* | 7/10 | 8/6 | 0.38 | 4/4 | 10/14 | 0.68 |
| Child–Pugh Class A/B, *n* | 16/1 | 13/1 | 0.89 | 8/0 | 22/2 | 0.40 |
| Median ALBI score (IQR) | −2.25 (−2.81, −2.05) | −2.06 (−2.50, −1.76) | 0.10 | −2.42 (−2.55, −2.18) | −2.51 (−2.78, −2.01) | 0.90 |
| ALBI grade 1/2a/2b/3, *n* | 7/1/9/0 | 1/3/9/0 | 0.08 | 1/4/3/0 | 10/3/10/1 | 0.13 |
| Median AFP(IQR), ng/mL | 8.7 (3.8, 30.5) | 26.1 (8.3, 111.6) | 0.34 | 1006.6 (14.2, 3634.2) | 20.0 (5.6, 822.7) | 0.29 |
| Median PIVKA-II(IQR), mAU/mL | 121(67, 335) | 112(64, 402) | 0.75 | 146(58, 3058) | 810(92, 4024) | 0.42 |
| Maximal tumor size >5/≤5 cm | 12/5 | 10/4 | 0.96 | 6/2 | 16/8 | 0.66 |
| Tumor number >3/≤3 | 13/4 | 8/6 | 0.25 | 3/5 | 12/12 | 0.95 |
| Vessel invasion, *n* | — | — | — | 4 | 10 | 0.68 |
| Extrahepatic metastasis, *n* | — | — | — | 4 | 18 | 0.19 |
| Median period from initial treatment to start of LEN (IQR), years | 2.0(0.8, 4.1) | 1.6 (1.3, 2.7) | 0.91 | 3.0(1.6, 4.5) | 2.3 (0.9, 7.0) | 0.76 |
| **Average number of TACE treatments before LEN** | 2.8 ± 1.3 | 2.5 ± 1.4 | 0.70 | **3.4 ± 1.3** | **2.0 ± 1.5** | **0.03** |

$p < 0.05$ are highlighted in bold.

[†]Comparison of patients with and without rechallenge TACE.

Abbreviations: ALBI, albumin-bilirubin; BCLC, Barcelona Clinic Liver Cancer; IQR, Inter Quartile Range; AFP, alpha-fetoprotein; LEN, lenvatinib; PIVKA-II, protein induced by Vitamin K absence or antagonists-II; TACE, transcatheter arterial chemoembolization.

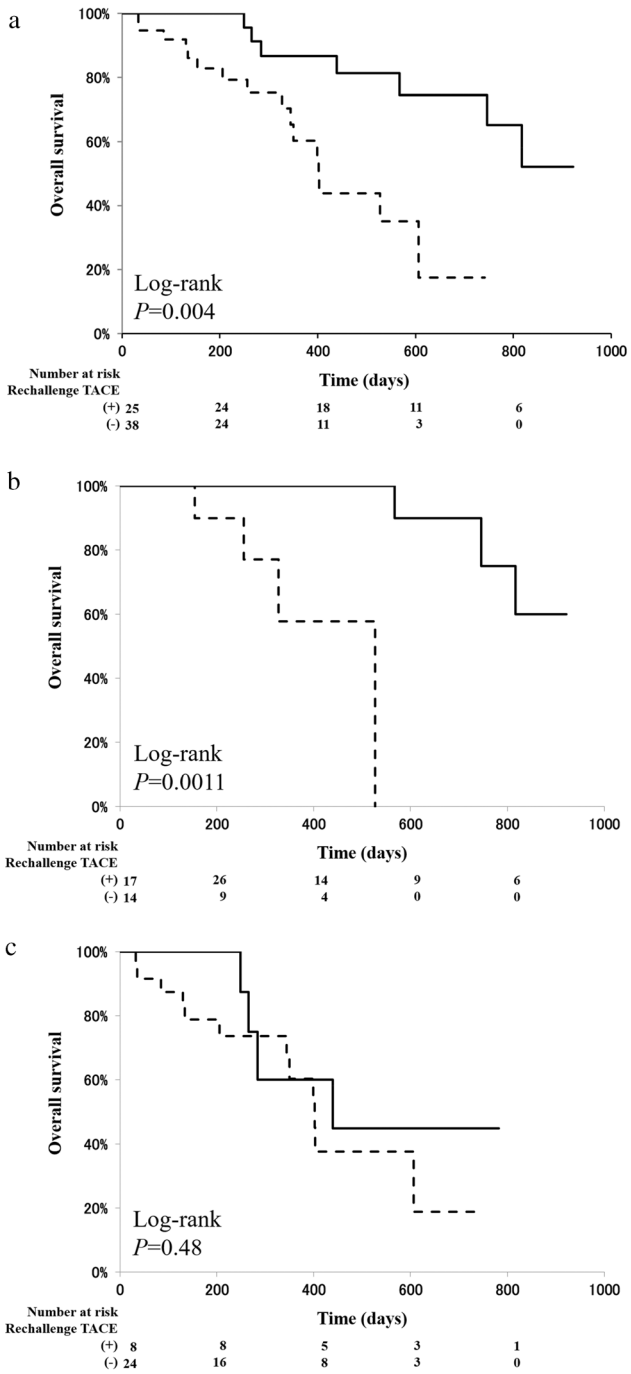


**Figure 2** Kaplan–Meier curves of overall survival (OS) in patients who underwent (solid line) and did not undergo (dotted line) rechallenge TACE. (a) OS of all 63 patients. (b) OS of BCLC stage A and B patients. (c) OS of BCLC stage C patients. BCLC, Barcelona Clinic Liver Cancer; TACE, transcatheter arterial chemoembolization ——, rechallenge TACE (+); ----- rechallenge TACE (−).

reached and 402 days, respectively, $P = 0.23$, Fig. S1c. ALBI-2, 3; 439 and 403 days, respectively, $P = 0.72$, Fig. S1d). In addition, the analysis was performed separately for the presence or absence of distant metastasis. In the group without distant metastasis, the rechallenge TACE group had a significantly longer median OS time than the non-rechallenge TACE group (not reached and 403 days, respectively, $P = 0.003$. Fig. S1e), but there was no significant difference in the group with distant metastasis (284 and 399 days, respectively, $P = 0.85$. Fig. S1f).

Rechallenge TACE significantly reduced the risk of death in univariate (hazard ratio [HR] 0.24, 95% confidence interval [CI] 0.08–0.69, $P = 0.008$) and multivariate analyses (HR 0.26, 95% CI 0.08–0.80, $P = 0.019$) (Table 2).

If CR + PR was achieved by patients who underwent rechallenge TACE, their median survival time was significantly longer than those of the PD group (not reached and 567 days, respectively, $P = 0.05$). The CR + PR group had significantly fewer intrahepatic lesions than the PD group ($P = 0.015$) (Table 3). The median survival time of the PD group after rechallenge TACE was not different from that of the group without rechallenge TACE (567 days and 402 days, respectively, $P = 0.36$).

***Changes in hepatic reserve before and after rechallenge TACE.*** Figure 3 shows changes in the ALBI score before and after rechallenge TACE among patients who underwent rechallenge TACE. No statistically significant difference was observed between any of the time points (Fig. 3).

***Case.*** A woman in her 70s was diagnosed with unresectable HCC in segment (S) 8 with portal vein tumor thrombus. She had previously been treated with hepatectomy, RFA, and TACE for HCC. TACE was performed twice for S8 HCC, but she was judged to be TACE-refractory. Therefore, she started LEN treatment, but her blood pressure control was poor, and she was LEN-intolerant. The effect of the LEN treatment was also very poor. After the LEN treatment for only 1 month rechallenge TACE was performed twice. The therapeutic effect of rechallenge TACE was very good, and CR was achieved (Fig. 4). The AFP level decreased from 24 489.9 ng/mL before rechallenge TACE to within the normal range after treatment. The patient has survived for 3 years without additional treatment or recurrence of HCC.

## Discussion

In this study, we describe the clinical course of 63 patients with unresectable HCC with a history of TACE failure/refractoriness before LEN treatment as a first-line systemic therapy. Among this population, 25 patients (39.7%) received rechallenge TACE after the LEN treatment, and 65% of these patients achieved CR or PR. TACE has also been reported to achieve objective responses in 16–61% of patients with HCC.[27–29] In our study, we targeted cases that were once judged to be TACE failure/refractoriness, and we believe that a very high objective response was confirmed. Moreover, patients in the rechallenge TACE group had a better OS than those in the group without rechallenge TACE. *Re*challenge TACE significantly reduces the risk of death. There was no decrease in the ALBI score after rechallenge TACE, and even if the effect of rechallenge TACE was poor, the prognosis of the patients did not deteriorate.

**Table 2** Univariate and multivariate Cox proportional hazards model analysis for overall survival (OS)

| | | Crude Hazard ratio | *P* value | Adjusted Hazard ratio | *P* value |
|---|---|---|---|---|---|
| Sex | Male | 1 [reference] | | 1 [reference] | |
| | Female | 0.67 (0.20–2.25) | 0.51 | 1.33 (0.07–1.45) | 0.14 |
| Age (years) | <70 | 1 [reference] | | 1 [reference] | |
| | ≥70 | 0.57 (0.24–1.40) | 0.11 | 0.96 (0.40–2.31) | 0.92 |
| Etiology | Viral | 1 [reference] | | 1 [reference] | |
| | Non-viral | 0.71 (0.29–1.72) | 0.45 | 0.65(0.27–1.55) | 0.33 |
| AFP (ng/mL) | <100 | 1 [reference] | | 1 [reference] | |
| | ≧100 | 1.26 (0.50–3.16) | 0.63 | 1.58 (0.55–4.52) | 0.39 |
| ALBI grade | 1 | 1 [reference] | | 1 [reference] | |
| | 2, 3 | 1.11 (0.44–2.80) | 0.82 | 1.67 (0.68–4.11) | 0.27 |
| **BCLC stage** | A, B | 1 [reference] | | 1 [reference] | |
| | **C** | **3.20 (1.21–8.48)** | **0.02** | 2.17 (0.75–6.27) | 0.15 |
| **Rechallenge TACE** | No | 1 [reference] | | 1 [reference] | |
| | **Yes** | **0.24 (0.08–0.69)** | **0.008** | **0.26 (0.08–0.80)** | **0.019** |

*P* < 0.05 are highlighted in bold.

*Note*: Adjusted variables: sex, age (<70 or ≥70), etiology (viral or nonviral), AFP (<100 or ≥100), ALBI grade (1, 2, or 3), BCLC stage (A, B, or C), and rechallenge TACE (yes or no). $p < 0.05$ are highlighted in bold.

Abbreviations: AFP, alpha-fetoprotein; ALBI, albumin-bilirubin; BCLC, Barcelona Clinic Liver Cancer; NA, not available; TACE, transcatheter arterial chemoembolization.

**Table 3** Comparison of patient backgrounds by rechallenge TACE

| | CR + PR ($n = 13$) | PD ($n = 7$) | *P* value |
|---|---|---|---|
| Median age (IQR), years | 76 (64, 78) | 75 (70, 80) | 0.61 |
| Sex, male/female | 10/3 | 7/0 | 0.17 |
| Etiology, viral/ nonviral | 6/7 | 1/6 | 0.15 |
| Child–Pugh Class A/B | 12/1 | 7/0 | 0.45 |
| Median ALBI score (IQR) | −2.39 (−2.81, 2.19) | −2.14 (−2.32, 2.03) | 0.12 |
| BCLC stage A, B/C | 9/4 | 5/2 | 0.92 |
| Vessel invasion, *n* | 2 | 1 | 0.95 |
| Extrahepatic metastasis, *n* | 2 | 1 | 0.95 |
| Median AFP, ng/mL (IQR) | 15.7 (3.6, 836.3) | 16.1(8.6, 297.0) | 0.81 |
| Median PIVKA-II, mAU/mL (IQR) | 139(67, 1522) | 335(183, 4056) | 0.32 |
| Median period from initial treatment to start of LEN, years (IQR) | 2.8 (1.7, 4.7) | 1.3 (0.8, 3.5) | 0.17 |
| Number of TACE treatments | 3.2 ± 1.3 | 3.0 ± 1.4 | 0.72 |
| Reason for rechallenge TACE LEN, refractory/intolerable | 10/3 | 4/3 | 0.36 |
| Treatment period for LEN until rechallenge TACE, days | 208.0 ± 195.0 | 167.4 ± 153.3 | 0.64 |
| Best response of LEN, CR + PR + SD/PD | 5/8 | 5/2 | 0.16 |
| maximal tumor size >5/≤5 cm | 9/4 | 5/2 | 0.92 |
| **Median number of liver lesions (IQR)** | **3 (1, 6)** | **15(6, 22)** | **0.015** |
| BCLC-B within up-to-7/B beyond up-to-7/C | 2/5/6 | 0/4/3 | 0.55 |

*P* < 0.05 are highlighted in bold.

Abbreviations: AFP, alpha-fetoprotein; ALBI, albumin-bilirubin; BCLC, Barcelona Clinic Liver Cancer; CR, complete response; IQR, inter-quartile range; LEN, Lenvatinib; PD, progressive disease; PIVKA-II, protein induced by Vitamin K absence or antagonists-II; PR, partial response; SD, stable disease; TACE, transcatheter arterial chemoembolization.

LEN is an effective treatment for TACE-refractory/unresectable HCC. However, tumor control with LEN alone is largely difficult, and LEN intolerance may require dose reduction or discontinuation due to AEs.[15–20] Recent research has suggested that LEN-TACE sequential treatment is effective for intermediate HCC and demonstrates an extension of OS in the LEN-TACE group compared with the LEN-alone group.[21–23] However, it has not been clear whether rechallenge TACE is effective after LEN treatment, for which past TACE administration has resulted in failure or refractoriness. In general, for LEN refractory/intolerant patients with maintained hepatic reserve, many of whom have been introduced LEN after TACE was refractory, other MTAs are selected for subsequent treatment.[30,31] Most of the subjects in our study were advanced HCC patients who had been introduced LEN

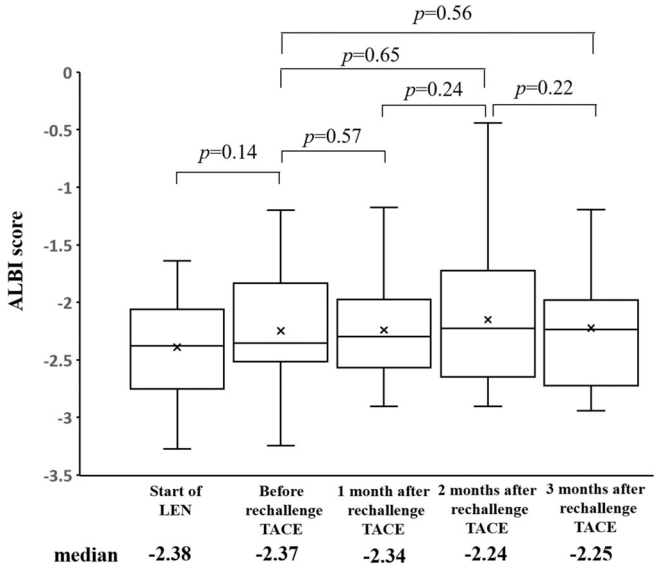


**Figure 3** Changes in the ALBI score before and after rechallenge TACE among patients who underwent rechallenge TACE. ALBI, albumin-bilirubin, LEN, lenvatinib; TACE, transcatheter arterial chemoembolization.

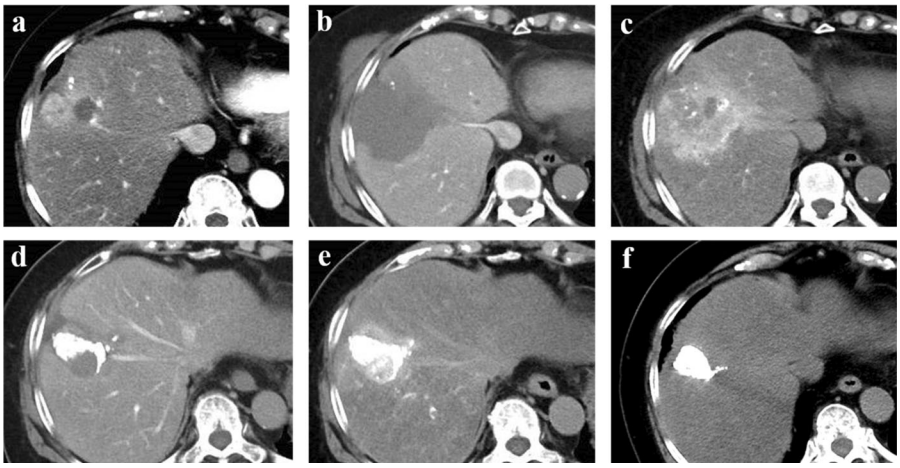


**Figure 4** Images before and after lenvatinib and rechallenge TACE in a patient with unresectable HCC with portal vein tumor thrombus. Arterial phase imaging of (a) contrast-enhanced computed tomography (CT) before lenvatinib, (b) CT during arterial portography (CTAP), and (c) CT during hepatic arteriography (CTHA) at the first rechallenge TACE. (d) CTAP and (e) CTHA at the second rechallenge TACE, and plain CT 2 years after the second rechallenge TACE. rechallenge TACE (+); rechallenge TACE (−).

after TACE was refractory. In fact, many of the patients without rechallenge TACE in this study were treated with other MTAs after LEN. However, in actual clinical practice, TACE may be an additional option even if the previous TACE was failure or refractoriness. Our study result showed that rechallenge TACE had a favorable outcome and improved prognosis, especially in patients with BCLC-A and B stage.

This study included cases of BCLC-C, and the recommended treatment for BCLC-C HCC is systemic therapy.[7] However, controlling intrahepatic lesions with TACE allows a more curative metastasis treatment and may prolong OS and improve the prognosis.[32–35] In this study, there were cases in which intrahepatic lesions were controlled by rechallenge TACE successively, and excision and radiotherapy were performed for lymph node metastases, resulting in CR. That is, LEN and rechallenge TACE may allow subsequent conversion treatments. Rechallenge TACE did not prolong OS in BCLC-C patients in this study. However, some BCLC-C patients also benefited from rechallenge TACE.

Tumor cells release angiogenic factors, such as vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), and fibroblast growth factor (FGF), which act on nearby

blood vessels, resulting in tumor angiogenesis.[36,37] These angiogenic factors lead to the rapid development of tumor neovascular vessels that are irregularly shaped, dilated, leaky, and fragile.[36] For this tumor environment, a new idea has recently been proposed, in which angiogenesis inhibitors remodel abnormal tumor vessels into normal vessels, referred to as "tumor vascular normalization".[38,39] Normalization improves the tumor microenvironment and inhibits tumor growth and metastasis.[40] In addition, normalization of tumor vessels also improves blood perfusion and tumor oxygenation in tumor tissues, which may enhance the efficacy of chemotherapy.[41,42] In other words, pretreatment with VEGF inhibitors promotes normalization of tumor vessels, intertumoral interstitial pressure, and vascular permeability.[39,43] Since both sorafenib and LEN are multi-target tyrosine kinase inhibitors, their ability to inhibit VEGF receptor (VEGFR), PDGF receptor (PDGFR), and FGF receptors (FGFR) varies; in particular, the inhibitory effect of LEN on VEGFR is higher than that of sorafenib.[44,45] Recently, Une *et al*. reported that LEN treatment induced vascular normalization and improved the intratumoral microenvironment in HCC tumors earlier and more effectively than sorafenib treatment.[46] This mechanism will improve the distribution of Lipiodol® mixed in combination with anticancer drugs and enhance the therapeutic effect of TACE. The effectiveness of combination therapy with sorafenib and TACE for HCC has been reported.[47] However, considering these results, the combination therapy with LEN and TACE is expected to be even more effective. Moreover, rechallenge TACE was very effective, even when the maximal effect of LEN treatment was PD. Rechallenge TACE is expected after atezolizumab plus bevacizumab, a recombinant humanized monoclonal antibody developed against VEGF, combination therapy, and the current first-line treatment for HCC.[14]

The limitations of this study include its retrospective nature and single-center design with a relatively small number of patients. The median follow-up period (approximately 12 months) was relatively short. Furthermore, various subsequent treatments were used because there is no established treatment strategy, and it was difficult to clarify the actual impact of each treatment with a small number of cases. Future studies using larger, multicenter cohorts with a sufficient observation period are required to validate these outcomes.

## Conclusion

Rechallenge TACE after LEN may be an effective treatment option for patients with unresectable HCCs, even in cases of previous refractory TACE.

***Data availability statement.*** All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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## Supporting information

Additional supporting information may be found in the online version of this article at the publisher's website:

**Figure S1.** Kaplan–Meier curves of overall survival in patients who underwent (solid line) and did not undergo (dotted line) rechallenge TACE
a. Overall survival of BCLC-A and B and ALBI-1 patients.
b. Overall survival of BCLC-A and B and ALBI-2 and 3 patients.
c. Overall survival of BCLC-C and ALBI-1 patients.
d. Overall survival of BCLC-C and ALBI-2 and 3 patients.
e. Overall survival of the patients without distant metastasis.
f. Overall survival of the patients with distant metastasis.
TACE, transcatheter arterial chemoembolization; BCLC, Barcelona Clinic Liver Cancer, ALBI, albumin-bilirubin.