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Efficacy and safety of lenvatinib–transcatheter arterial chemoembolisation sequential therapy followed by surgical resection for intermediate-stage hepatocellular carcinoma beyond Up-to-7 criteria: a study protocol for a multicentre, single-arm, prospective study

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ABSTRACT

Introduction The feasibility and efficacy of surgical resection following systemic therapy for intermediate-stage hepatocellular carcinoma (HCC) beyond the Up-to-7 criteria is unclear. The combination of lenvatinib (LEN) and transcatheter arterial chemoembolisation (TACE), termed LEN–TACE sequential therapy, has shown a high response rate and survival benefit in patients with intermediate-stage HCC. This trial aims to evaluate the efficacy and safety of LEN–TACE sequential therapy and the feasibility of surgical resection for intermediate-stage HCC beyond the Up-to-7 criteria.

Methods and analysis This is a multicentre, single-arm, prospective clinical trial. Thirty patients with intermediate-stage HCC beyond the Up-to-7 criteria will be enrolled. Patients eligible for this study will undergo LEN–TACE sequential therapy in which LEN is administered for 4 weeks, followed by TACE, and then further LEN for another 4 weeks. Patients will be assessed for efficacy of LEN–TACE sequential therapy and resectability, and surgical resection will be performed if the HCC is considered radically resectable. The primary outcome of this study is the resection rate after LEN–TACE sequential therapy. The secondary outcomes are the objective response rate of LEN–TACE sequential therapy, safety, curative resection rate, overall survival and recurrence-free survival.

Ethics and dissemination This trial was approved by the Institutional Review Board of Hiroshima University, Japan (approval no. CRB210003), and has been registered with the Japan Registry of Clinical Trials (jRCTs061220007). The results of this study will be submitted for publication in a peer-reviewed journal and shared with the scientific community at international conferences.

Trial registration number jRCTs061220007 (https://jrct.niph.go.jp/latest-detail/jRCTs061220007).

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This trial aims to investigate the efficacy and safety of lenvatinib (LEN)–transcatheter arterial chemoembolisation (TACE) sequential therapy and the feasibility of surgical resection for intermediate-stage hepatocellular carcinoma (HCC) beyond the Up-to-7 criteria.
⇒ Eligible patients will receive 4 weeks of LEN and TACE treatment, followed by another 4 weeks of LEN; treatment efficacy and safety and the feasibility of surgical resection will subsequently be evaluated.
⇒ This is a multicentre, single-arm, open-label, prospective clinical trial.
⇒ A limitation of this study is that it may have biases in terms of patient selection and evaluation of outcomes due to the single-arm design.

INTRODUCTION

Hepatocellular carcinoma (HCC) is the sixth most common cancer and third leading cause of cancer-related deaths with approximately 0.8 million patients dying from HCC.[1] The Barcelona Clinical Liver Cancer (BCLC) staging system and the Milan criteria are used worldwide to define a treatment algorithm for HCC.[2] Among the stages in BCLC, intermediate-stage HCC is defined as HCC that does not meet the Milan criteria and shows no vascular invasion or extrahepatic spread. It has been recommended that patients with intermediate-stage HCC undergo transcatheter arterial chemoembolisation (TACE),

however, TACE is not effective in all patients, due to background heterogeneity.[2 3] Several approaches have been attempted to subclassify intermediate-stage HCC to establish a treatment strategy. In subclassifications, the Up-to-7 criteria, which are defined as whether the sum of the number of tumours and the greatest diameter exceeds 7, are used as an indicator to reflect tumour burden and volume.[4 5] TACE for patients with intermediate-HCC beyond the Up-to-7 criteria resulted in poor liver function and poor prognosis.[6 7]

Several investigators have reported that surgical resection for intermediate-stage HCC significantly improves overall survival (OS), as compared with TACE, and surgical resection is one viable treatment option.[8 9] However, liver resection has not shown any benefit over other treatments in terms of survival in patients with a large tumour burden.[10 11] Moreover, our previous study showed that liver resection significantly prolonged OS, as compared with TACE, in patients with intermediate-stage HCC within the Up-to-7 criteria, while there was no significant difference in patients with HCC beyond the Up-to-7 criteria.[12] Intermediate-stage HCC beyond the Up-to-7 criteria is considered technically unresectable in many cases; further, resection is unsuitable as the initial treatment.

In the REFLECT trial, lenvatinib (LEN) showed a significantly higher objective response rate (ORR) and better progression-free survival (PFS) than sorafenib, a conventional standard chemotherapy.[13] LEN is a multikinase inhibitor that targets vascular endothelial growth factor (VEGF) receptors 1–3, fibroblast growth factor (FGF) receptors 1–4, platelet-derived growth factor receptor-α, rearranged during transfection, and KIT is one of the approved first-line treatments for patients with advanced HCC.[14] Kudo *et al* showed that LEN was significantly better than TACE as an initial therapy for intermediate-stage HCC beyond the Up-to-7 criteria, in terms of both response rate and survival.[15] However, LEN often requires early drug discontinuation or dose reduction due to adverse events. To reduce adverse events associated with continuous administration and increase the acceptability of LEN, LEN–TACE therapy, in which LEN and TACE are alternated, has been developed and shown to be effective. Ando *et al* reported that LEN–TACE sequential therapy showed a high ORR of 63.2% and significantly improved OS and PFS as compared with LEN alone in intermediate-stage HCC.[16] Shimose *et al* also showed that the survival rate of the alternating LEN and TACE group was significantly higher than that of the LEN alone group.[17] Kuroda *et al* reported that OS and PFS of patients treated with LEN–TACE sequential therapy for unresectable HCC were significantly extended compared with those treated with LEN alone, with a high ORR of 74.1% in intermediate-stage HCC.[18] In addition, Ando *et al* and Kuroda *et al* reported that there were no significant changes in the albumin-bilirubin (ALBI) score during LEN–TACE sequential therapy, with minimal liver dysfunction.[16 18]

Although LEN–TACE sequential therapy is highly effective, complete response rate has been reported to be up to 20.6%, and tumour progression and new lesions may occur due to the acquisition of resistance. Recently, favourable results of conversion surgery, a surgical procedure to achieve radical cure after non-surgical treatment for unresectable HCC, after LEN for unresectable HCC have been reported.[19 20] Shindoh *et al* reported that radical resection after LEN for unresectable HCC is an independent factor for prolonged disease-specific survival.[21] However, the impact of surgical resection following systemic therapy for intermediate-stage HCC beyond the Up-to-7 criteria is unclear. We hypothesised that the curative surgical resection after systemic therapy for intermediate-stage HCC beyond the Up-to-7 criteria may be effective. LEN–TACE sequential therapy may be advantageous as a preoperative treatment because it has high anti-tumour efficacy, causes minimal liver dysfunction and does not require long drug-off periods.

This study aims to evaluate the efficacy and safety of LEN–TACE sequential therapy and the feasibility of surgical resection after LEN–TACE sequential therapy for intermediate-stage HCC beyond the Up-to-7 criteria.

METHODS AND ANALYSES

Study design

This multicentre, single-arm, prospective clinical study will be conducted between 13 April 2022 and 31 January 2027. Five hospitals belonging to the Hiroshima Surgical Study Group of Clinical Oncology (HiSCO) have been registered as study sites. The study protocol was issued on 10 August 2022, and the number of amendments was one. The protocol was approved by the institutional review board of Hiroshima University, Japan (approval no. CRB210003).

Informed consent

Thirty patients with intermediate-stage HCC beyond the Up-to-7 criteria will be enrolled in the study. For inclusion, all patients will first need to provide written informed consent after receiving a detailed verbal explanation of the study protocol. The informed consent document is available in its original language (Japanese) as an online supplemental file 1. This explanation will include the purpose of the trial, a detailed method for examinations and treatments and a list of possible adverse events or risks associated with the intervention. Patients will also be informed that they can withdraw from the study at any time, for any reason and without any disadvantages to their future treatment. No patient will participate in the trial without implementation of the formal informed consent procedure.

The inclusion criteria for the study are as follows: (1) age ≥20 years, (2) no history of chemotherapy for HCC, (3) Eastern Cooperative Oncology Group Performance Status 0–1, (4) Child-Pugh score 5–6, (5) adequate organ function as defined by a white blood cell count ≥3.0×10^9/L,

neutrophil count ≥1.5×10^9/L, haemoglobin ≥85 g/L, platelet count ≥75×10^9/L, total bilirubin ≤2.0 mg/dL, albumin ≥2.8 g/dL, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤5 times the institutional standard, creatinine clearance >40 mL/min and proteinuria ≥2+, (6) absence of any other active malignant disease, (7) documented consent for participation in this study, (8) classification as intermediate-stage HCC by the BCLC classification defined as two to three nodules ≥3 cm or four or more nodules without vascular invasion and extrahepatic metastasis,[33] (9) beyond the Up-to-7 criteria, (10) no more than one prior TACE, (11) no previous liver lobectomy and (12) no more than 10 tumours.

Inclusion and exclusion criteria

The exclusion criteria are as follows: (1) refractory pleural effusion or ascites, (2) hepatic encephalopathy, (3) serious complications, such as seizures and paroxysmal disease, New York Heart Association class II or higher congestive heart failure, serious psychiatric illness, allergic reaction to contrast media that could interfere with angiography, uncontrolled hypertension, active bleeding, (4) a history of cardiovascular disease and thromboembolism within 6 months prior to enrolment, or arrhythmia requiring treatment, (5) pregnancy or lactation, or potential pregnancy, (6) difficulty in oral intake, (7) active infections other than hepatitis virus infection, (8) human immunodeficiency virus-positivity, (9) pulmonary fibrosis or interstitial pneumonia, (10) blood transfusion or administration of granulocyte-colony stimulating factor within 14 days prior to enrolment, (11) a general condition judged to make them ineligible for participation in the study according to the attending physician, (12) inability to undergo contrast-enhanced CT or MRI, (13) participation or intention to participate in other clinical studies concurrently with this study, (14) likelihood to interfere with, limit or confuse the specific evaluation to the clinical research protocol and (15) employment by the principal investigator who is directly involved in this or other clinical research, or by the implementing medical institution.

Study procedures

The participant registration for the study will run from April 2022 to April 2026. The diagnosis of HCC will be confirmed using CT or MRI. Additional hepatic arterial angiography will be performed as needed. Informed consent will be obtained from patients diagnosed with HCC who meet the eligibility criteria for the study.

The procedure for LEN–TACE sequential therapy has been described previously.[16] LEN will be administered orally, at a dose of 12 mg once daily for patients weighing 60 kg or more, and a dose of 8 mg once daily for patients weighing less than 60 kg, for 4 weeks. After 4 weeks of treatment with LEN, TACE will be performed. LEN will be interrupted for at least 2 days before and after TACE. For TACE, angiography will be performed to confirm the site of HCC and the feeding artery, followed by intra-arterial injection of lipiodol and epirubicin, cisplatin or miriplatin, and injection of an embolic agent, Gelpart (Nippon Kayaku, Tokyo, Japan) to interrupt blood flow. After confirming that the criteria for using LEN after TACE are met, administration of LEN will be resumed; if not, resumption of LEN administration will be postponed. The criteria for the administration of LEN after TACE are as follows: (1) no foreseeable risk of compromising the safety of the subject due to Common Terminology Criteria for Adverse Events (CTCAE) V.5.0 grade 2 or higher adverse events attributable to TACE; (2) adequate organ function, as indicated by haemoglobin ≥ 85 g/L, neutrophil count ≥1.5×10^9/L, platelet count ≥75×10^9/L, total bilirubin ≤2.0 mg/dL, ALT and AST ≤5 times the institutional standard and creatinine clearance >40 mL/min. LEN will be administered for an additional 4 weeks, followed by contrast-enhanced CT or MRI, to determine the efficacy of LEN–TACE sequential therapy. The efficacy will be evaluated by RECIST V.1.1 and modified RECIST.[22 23] Patients who are judged to be unable to continue LEN–TACE due to adverse events or tumour progression will be withdrawn from the trial and converted to other treatments considered most suitable.

In addition to the efficacy of imaging, the general condition and organ function of patients will be measured to determine whether liver resection is feasible. The criteria for liver resection are as follows: (1) patients are not judged as having progressive disease based on imaging evaluation, (2) Child-Pugh score ≤6, (3) patients with sufficient residual liver volume to avoid postoperative liver failure after liver resection, (4) resection with a negative margin is expected to be possible, (5) adequate organ function as indicated by haemoglobin ≥85 g/L, neutrophil count ≥1.5×10^9/L, platelet count ≥75×10^9/L, total bilirubin ≤2.0 mg/dL, ALT and AST ≤5 times the institutional standard and creatinine clearance >40 mL/min. A standard liver resection procedure, as previously reported, will be used in this study.[24 25] Patients who meet the criteria for resection will undergo surgical resection. The type of hepatic resection will be selected based on liver function, tumour extent and residual liver volume. Liver function will be evaluated by Child-Pugh score and indocyanine green retention at 15 min (ICG-R15). The estimated residual liver volume will be measured by CT volumetry using SYNAPSE VINCENT (Fujifilm Medical, Tokyo, Japan). In patients with adequate liver function and residual liver volume, anatomical hepatectomy will be performed basically. Patients with inadequate hepatic reserve function or inadequate residual liver volume will undergo limited resection. Preoperative evaluation and selection of the procedure will be performed by surgeons who routinely perform liver resections. No restrictions will be placed on the surgical approach. Respiratory training, nutritional management and blood glucose control will be provided preoperatively as needed. LEN will be discontinued at least 1 week prior to surgery and will not be resumed postoperatively.

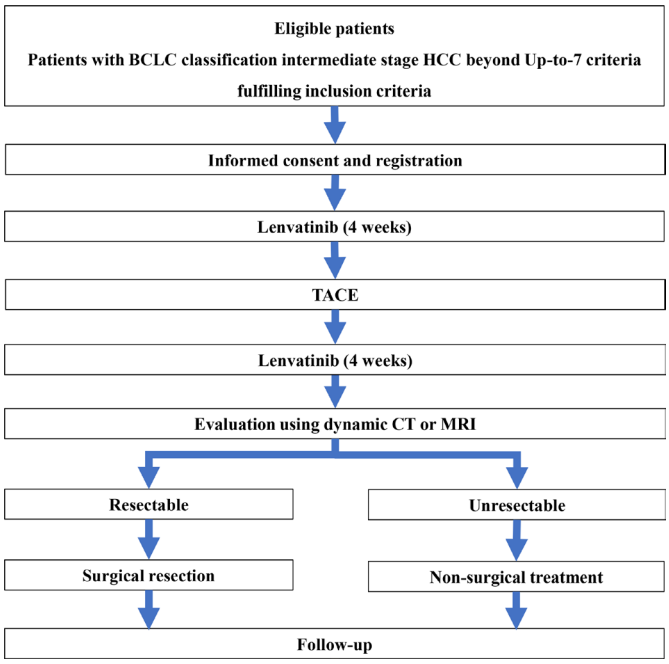

Figure 1 Flowchart of study design. BCLC, Barcelona Clinic Liver Cancer; HCC, hepatocellular carcinoma; TACE, transcatheter arterial chemoembolisation.

This study will not prescribe any postoperative management methods. General management, as in routine liver resection, will be performed at each institution. Postoperative follow-up will be performed in accordance with conventional medical practice at each institution. Complications that occur during the first 90 postoperative days will be recorded.

Patients who will not meet the criteria for resection will be considered unresectable and will receive non-surgical treatment, as determined by the treatment team. Unresectable HCC in this study will be defined as technically unresectable disease with inability for macroscopic radical resection or oncologically unresectable diseases that are uncontrollable with LEN–TACE sequential therapy. All decisions will be made by the local multidisciplinary clinical team, including assessment of efficacy and decisions regarding treatment continuation. The outcome of all patients will be studied 6 months after the last patient completes the protocol intervention. The flow of the study is illustrated in figure 1.

Study endpoints

The primary endpoint is the proportion of patients who undergo liver resection after LEN–TACE sequential therapy. The secondary endpoints are the ORR to LEN–TACE sequential therapy, curative resection rate, OS of the entire patient cohort and relapse-free survival (RFS) after resection. ORR is defined as the rate of patients with a partial or complete response. OS is defined as the time from registration to death by any cause.

The safety endpoints of the study will be the frequency and severity of adverse events of LEN–TACE sequential therapy. Severity will be determined according to the CTCAE V.5.0. In addition, a change in liver functional reserve before and after LEN–TACE therapy will be analysed using the factors included in the ALBI score and ICG-R15. Perioperative mortality and morbidity severity will be defined according to the Clavien-Dindo classification. In the event of serious complications involving long-term hospitalisation or death, the investigator will promptly report the case to the Committee for the Promotion of Regenerative Medicine and the Ministry of Health, Labor, and Welfare.

Sample size

In our previous study, which was conducted prior to the approval of LEN, the proportion of patients who underwent surgical resection was 39.1% among patients with intermediate-stage HCC beyond the Up-to-7 criteria, while the percentage of patients with technically resectable HCC at diagnosis is estimated to be about 30%.[12] The rate of patients who underwent surgical resection after LEN treatment for unresectable HCC is reported to be 14.9%.[21] The ORR of LEN–TACE sequential therapy is comparable to that of LEN alone, and the proportion of patients judged resectable by the criteria of this study after LEN–TACE sequential therapy was estimated to increase by 20%. Assuming that 30% of patients are technically resectable without prior treatment and that 50% are judged to be resectable after pretreatment, the number of cases needed to verify is 27, assuming a two-sided significance level (α error) of 0.10 and a power (1–β) of 0.80. Thus, we have chosen to target a sample size of 30 patients, considering a 10% discontinuation or dropout rate. Five facilities are scheduled to participate in this study, and no upper limit has been set for the number of patients who may be enrolled in each facility.

Statistical analysis

In this study, the target population for the analysis is defined as a full analysis set (FAS). FAS is defined as the population of all enrolled patients excluding cases that will not meet the eligibility criteria. Patient characteristic data will be expressed as median (range). For items observed as discrete values, the number of examples in each category and their proportions will be calculated using summary statistics. Statistical tests for the main analysis will be performed at a two-tailed 5% significance level. Time-to-event data, including OS and RFS, will be calculated using the Kaplan-Meier method. Patients in whom no event has been confirmed at the time of analysis will be censored based on the last recorded date of event occurrence confirmation. Safety data, including the type, incidence and severity of adverse events, which are defined by CTCAE V.5 or Clavien-Dindo classification, will be monitored, documented and reported as described in this protocol. All statistical analyses will be performed using JMP software (V.16.0; SAS Institute, Cary, North Carolina, USA). Statistical significance is defined by a p value<0.05.

Data management and monitoring plan

All electronic data recorded at each institution will be collected. The registration of an electronic data capture system (REDCap) will be used for central registration using identification. Only the authorised staff at each facility will have access via an individual secure login with username and password to enter the data. The principal investigator will monitor data input to ensure quality control. The principal investigator will designate a person in charge of monitoring to confirm that this research is conducted safely, in accordance with the research protocol and clinical research methods, and that data are being collected accurately. The person in charge of monitoring will submit the results to the principal investigator.

Patient and public involvement

Neither the patients nor the public were involved in setting the research questions, recruiting patients or conducting the study.

Ethics and dissemination

This trial has been approved by the institutional review board of Hiroshima University, Japan (approval no. CRB210003) and is registered with the Japan Registry of Clinical Trials (jRCTs061220007). The principal investigator reviewed all documents communicating with the ethics committee. Modifications to the protocol will be reviewed by the ethics committee and will be implemented after their approval. This study adheres to the principles of the 1975 Declaration of Helsinki. The results of the primary and secondary endpoints will be submitted for publication in peer-reviewed journals. The datasets used in this study will be available from the corresponding author on reasonable request.

DISCUSSION

Although sorafenib was used as the first-line systemic therapy for HCC before LEN had been approved, its ORR was low (12.4%), and few cases of conversion surgery had been reported. In contrast, LEN has demonstrated an ORR of 40.6% for advanced-stage HCC, which is significantly higher than that of sorafenib.[13] With the development of highly effective anti-tumour agents, the efficacy of conversion surgery for unresectable HCC has been increasingly reported.[21]

Surgical resection for intermediate-stage HCC with a high tumour volume, such as HCC beyond the Up-to-7 criteria, has not shown any survival benefits over other treatments, and such tumours are considered unsuitable for resection. Wada *et al* reported that the number of tumours was an independent prognostic factor and that the indication of surgery for intermediate-stage HCC with more than four tumours should be carefully determined.[10] In our previous study, the OS results for the resection and non-resection groups were not significantly different.[12] However, Kudo *et al* showed an extremely high ORR of 73.3% for LEN in intermediate-stage HCC beyond the UP-to-7 criteria, indicating a high potential for tumour shrinkage and down staging in such cases.[15] As no prospective studies have focused on the feasibility and efficacy of resection after systemic therapy in patients with intermediate-stage HCC unsuitable resection, we designed this trial to investigate this question.

In this study, LEN–TACE sequential therapy will be performed as the initial treatment. LEN is the only treatment that has been demonstrated to be more effective than TACE for intermediate-stage HCC beyond the Up-to-7 criteria.[15] However, its high incidence of adverse events and the low relative dose intensity may lead to discontinuation of LEN and poor patient prognosis.[26] To maintain a deep response of LEN without a decrease in liver function and to treat tumours that are not controlled by LEN alone, LEN–TACE sequential therapy was developed as a new treatment strategy. It has been reported that liver tissue injury induces hypoxia and promotes tumour angiogenesis and the hypoxia caused by TACE-induced ischaemia increases the serum VEGF and FGF levels, which promote angiogenesis.[27] In addition, a further increase in VEGF levels after TACE has been associated with worse prognosis, and the combined use of TACE and angiogenesis inhibitors has been revealed to increase antitumour efficacy significantly, as compared with the use of either treatment alone.[28 29] The TACTICS trial, a randomised phase II trial of molecular-targeted agents and TACE conducted in Japan, demonstrated the benefit of using sorafenib in combination with TACE.[30] LEN–TACE sequential therapy was selected in this study because of its rapid and high tumour response for intermediate-stage HCC and minimal impairment of hepatic reserve function.

In LEN–TACE sequential therapy, the duration of LEN treatment has not been established. Low relative dose intensity may be associated with prognosis, and it is important to reduce the number of patients requiring dose reduction or treatment discontinuation. The response of LEN is rapid, with an ORR of more than 50% reported after 2 weeks of treatment, suggesting that more than 2 weeks of treatment is necessary.[31] In addition, the median time to first dose reduction of LEN was reported to be 10.3 weeks in the REFLECT trial and we estimated that LEN for 8 weeks could be administered safely.[13] However, some patients discontinue or interrupt LEN after six consecutive weeks of administration in our experience. Therefore, to conduct treatment safely and effectively, LEN will be administered for 4 weeks before and after TACE, for a total of 8 weeks.

To evaluate the feasibility and efficacy of surgical resection after systemic therapy for intermediate-stage HCC beyond the Up-to-7 criteria, this study aims to investigate the efficacy and safety of LEN–TACE sequential therapy and resectability after LEN–TACE sequential therapy. The results of this study may allow more beneficial treatment strategies to be developed for patients with intermediate-stage HCC. This study was registered

with the Japan Registry of Clinical Trials, and patient recruitment began on 13 April 2022.

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