Study Protocol for a Trial: A Single-Arm, Open-Labeled Study Evaluating Transcatheter Arterial Embolization Plus Everolimus Combination Therapy for Patients With Liver Metastasis of Gastroenteropancreatic Neuroendocrine Tumors

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ABSTRACT

BACKGROUND: The number of patients with non-functional neuroendocrine tumors (NETs) has increased recently, and the rate of liver metastasis of NETs is about 20% in patients at the first diagnosis. Transcatheter arterial embolization (TAE) and everolimus are therapies with reported efficacy, but few reports have described their combined treatment. We therefore aim to evaluate the efficacy and safety of combination therapy with everolimus and TAE in patients with liver metastasis of gastroenteropancreatic neuroendocrine tumors (GEP-NETs) in a prospective study.

METHODS: We design a single-arm, open-label, prospective study to evaluate the efficacy and safety of combination therapy with everolimus and TAE in patients with liver metastases of GEP-NETs. The study started in June 2021 at Okayama University Hospital and is expected to enroll 18 patients over a 2-year period.

DISCUSSION: This study is a prospective study investigating a new treatment method for a rare disease called GEP-NETs. We may obtain useful information that contributes to the treatment guidelines in this study. However, NET is a rare disease, and although the number of cases is statistically established, it may not be possible to accurately assess causality.

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Introduction

Neuroendocrine neoplasms (NENs) are rare neoplasms, accounting for only new 3 to 5 patients per 1000 people. They mainly develop in the digestive organs, especially the pancreas and gastrointestinal tracts.

According to an epidemiological survey conducted in Japan, the number of patients with non-functional NENs has increased recently.[1] Possibly reasons for this uptick include NENs becoming more widely known among general clinicians and advances in the quality of diagnostic imaging.

According to the World Health Organization (WHO) classification criteria, NENs are categorized into well-differentiated neuroendocrine tumors (NETs) and poorly differentiated neuroendocrine carcinomas (NECs). Neuroendocrine tumors are further categorized into G1, G2, and G3 lesions based on the Ki-67 staining index or mitotic index.[2] Neuroendocrine neoplasms also demonstrate a variety of degrees of malignancy, and treatment methods are consequently diverse as well.

The liver metastasis rate of NETs is about 20% in patients at the first diagnosis. According to the guideline, multimodal therapy is recommended when patients have liver metastasis.[3-5] Transcatheter arterial embolization (TAE) is one therapy with reported efficacy.[6,7] Previous reports concerning TAE for liver metastasis of NETs have shown that the median progression-free survival (PFS) is 12 to 25 months,[6,8-11] the 5-year survival rate is 13% to 37%, and the median overall survival (OS) is 18 to 43 months.[7-11] Furthermore, in a recent Japanese report, the response rate was 56%, disease control rate (DCR) was 96%, and OS was 86.1 months.[8]

Other therapies aside from TAE have also been approved for NETs in Japan, including anti-tumor drugs, such as everolimus (mammalian target of rapamycin [mTOR] inhibitor), sunitinib (molecular-targeted drug), streptozocin (antineoplastic drug), and octreotide or lanreotide (synthetic somatostatin analogue). Everolimus inhibits mTOR, a serine-threonine kinase that stimulates cell growth, proliferation, and angiogenesis.[12-14] Autocrine activation of the mTOR signaling pathway,

mediated through insulin-like growth factor 1, has been implicated in the proliferation of pancreatic NET cells.[15]

The RADIANT-3 Clinical Trial confirmed the efficacy of everolimus in patients with advanced pancreatic NETs. Median PFS was 11.0 months in the everolimus arm and 4.6 months in the placebo arm (hazard ratio for disease progression or death from unknown cause: 0.35 for everolimus; 95% confidence interval [CI], 0.27-0.45; $P < .001$).[16] The RADIANT-4 Clinical Trial was also conducted in patients with advanced NETs of the lung or gastrointestinal tract and showed a median PFS of 11.0 months (95% CI, 9.2-13.3 months) in the everolimus arm and 3.9 months (95% CI, 3.6-7.4 months) in the placebo arm. The efficacy of everolimus was demonstrated.[17]

Given the above findings, everolimus has become widely used in NET therapy. However, there are no clear guidelines concerning the order of use of anti-tumor agents, including everolimus, and when to perform TAE. The treatment policy therefore varies among facilities. Combination therapy with anti-tumor agents and TAE is thus not often implemented because of a lack of reports concerning its efficacy, and the potential interaction mechanism between the 2 treatment approaches is not clear. We have treated 8 NET patients with liver metastases with a combination of chemotherapy and TAE. Although the results have not been published due to lack of treatment conditions and small number of patients, the results are good with an objective response rate of 63% and a PFS of 11 months.

We therefore aim to evaluate the efficacy and safety of combination therapy with everolimus and TAE in patients with liver metastasis of gastroenteropancreatic neuroendocrine tumors (GEP-NETs) in a prospective study.

Methods and Analysis

Objective

The objective of this study is to explore the efficacy and safety of TAE combined with everolimus in patients with liver metastasis of GEP-NETs.

Study setting

This study is a single-center, single-arm, open-label, prospective study.

Endpoints

The primary endpoint is the overall response rate (ORR) after combination therapy. The secondary endpoints are the PFS after everolimus introduction, DCR, OS, and rate of adverse events over grade 3.

We evaluate the endpoints based on the findings of contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) and a blood examination, which are performed every 3 months following combination therapy. Treatment efficacy is assessed by RECIST ver1.1 and modified RECIST.

Patients keep a daily record of any symptoms, and safety is assessed according to CTCAE v5.0.

Eligibility criteria

- Inclusion criteria:
  - Patients diagnosed with non-functional GEP-NETs confirmed pathologically
  - Patients with liver metastatic tumors and no treatment history of TAE or chemotherapy
  - Patients ⩾20 years old, regardless of sex
  - Patients who have provided their fully informed consent
  - Patients with a performance status 0 or 1
  - Patients with an adequate hematologic and end-organ function.

- Exclusion criteria:
  - Patients with a tumor thrombus or thrombus in the main and/or first portal vein
  - Patients with moderate or severe ascites
  - Patients with severe arteriovenous shunt in the liver
  - Patients with an allergy to contrast media
  - Patients with an estimated glomerular filtration rate (eGFR) <30 mL/min
  - Patients with an allergy to everolimus, sirolimus, or sirolimus derivatives
  - Patients with an allergy to gelatin
  - Patients with a treatment history of mTOR inhibitor
  - Patients with a more than 1 year of treatment of corticosteroids or other immunostimulatory agents
  - Patients with significant cardiovascular, infectious, diabetic, or pulmonary disease
  - Patients with a fasting glycemic level of ⩾1.5 ULN at the start of the screening period
  - Patients with interstitial pneumonia on CT
  - Patients who are pregnant or possible pregnant
  - Patients deemed not suitable for chemotherapy
  - Patients deemed inappropriate candidates by the chief medical examiner.

Treatment

In the TAE phase, the hepatic artery that supplies the tumor with nutrients is catheterized and selectively embolized using embolizing material. The study embolic agent is an embosphere containing 100 to 300 μm embolic beads. The agent is injected until substantial slowing of the blood flow is achieved. If liver tumors are widespread or huge and unable to be treated in a single session, TAE can be performed over 2 sessions.

Once the adverse events of TAE have improved to grade ⩽1, everolimus is administered within 2 months after

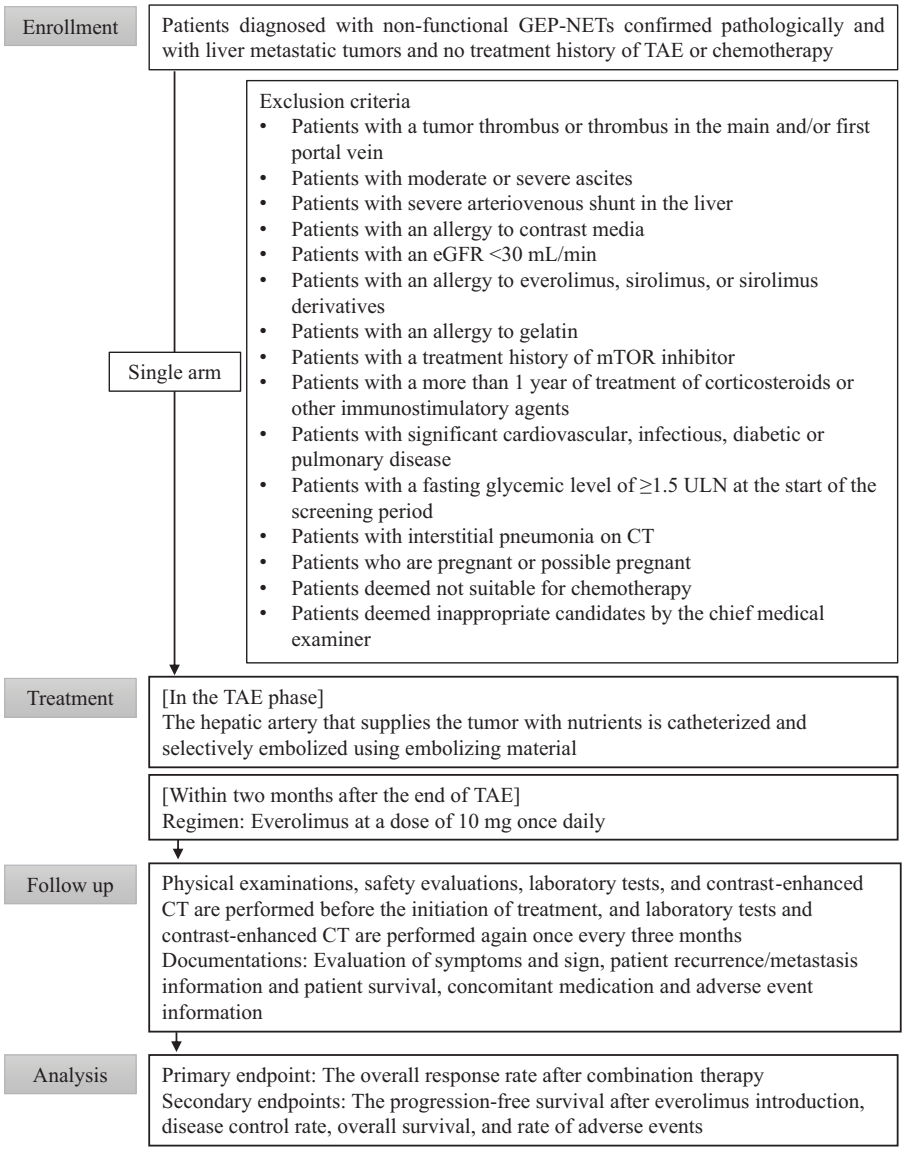

Figure 1. Flowchart of study. CT indicates computed tomography; eGFR, estimated glomerular filtration rate; GEP-NET, gastroenteropancreatic neuroendocrine tumor; mTOR, mammalian target of rapamycin; TAE, transcatheter arterial embolization.

the end of TAE. If everolimus is not started within 2 months, it will drop out. The trade name for everolimus used is Afinitor, and the dosage form is a tablet containing 5 mg of the ingredient in each tablet. The study drug is the mTOR inhibitor everolimus at a dose of 10 mg once daily. Patients continue the therapy until death or if one of the following criteria was met for the cessation of therapy: progressive disease following treatments, adverse events that required termination of treatment, deterioration of Eastern Cooperative Oncology Group Performance Status (ECOG PS) to 4, worsening liver function (Child-Pugh score ⩾ 10), or withdrawal of consent. In accordance with the protocol[18] and the accompanying documentation, dosing is delayed or reduced if patients develop an adverse event that is considered to be related to the study drug. Dose reductions of the study drug is allowed up to 2 times, initially up to 5 mg per day and then up to 5 mg every other day.

There are no specific recommendations regarding chemotherapeutic therapy after the completion of protocol treatment.

Follow-up

Physical examinations, safety evaluations, laboratory tests (blood tests, biochemistry tests, coagulation tests, and tumor markers), and contrast-enhanced CT are performed before the initiation of treatment, and laboratory tests and contrast-enhanced CT are performed again once every 3 months. After the study period, patient-reported outcomes are collected (Figure 1). Data such as evaluation of symptoms and sign,

patient recurrence/metastasis information and patient survival, concomitant medication, and adverse event information will be entered and managed in the designated Electronic Data Capture (EDC). Because the measurement of everolimus blood levels is not performed in general clinical practice, it will not be performed in this study.

Patient and public involvement

No patient involved.

Study design and statistical analyses

This study is a single-arm, open-label, prospective study designed to evaluate the efficacy and safety of combination therapy with TAE and everolimus at 10 mg/day. If the PFS in the combination therapy group is significantly higher than that in the everolimus-alone therapy group, the combination therapy may be able to suggest as one of the means of GEP-NETs treatment. Based on the results of previous clinical trials (RADIANT-3 and RADIANT-4), an ORR < 34% is considered to be unacceptable compared with standard treatment (everolimus alone).

The required sample size is calculated to be 18 patients for the study to have a power of 80%, assuming that an ORR rate of 64%, adding the effect of TAE based on the results of previous clinical studies, in combination therapy, and also assuming a 1-sided significance level of .05% and 10% ineligible cases. If a response is obtained in 11 patients, the point estimate will be 0.6875 (95% CI, 0.4133794-0.88983), which is a significant result. A total of 18 patients are planned to be enrolled over a period of 2 years. Data from missing or difficult-to-trace cases will not be used for analysis.

Discussion

To our current knowledge, the treatment strategy for patients with liver metastases of GEP-NETs has not been completely unified. In particular, there is not enough knowledge about combination therapy. This study is a single-center, single-arm, open-label, prospective study investigating a new treatment method for a rare disease called GEP-NETs. We may obtain useful information that contributes to the treatment guidelines in this study. However, this study has its limitations. As NET is a rare disease, this study is an open-label, uncontrolled study. Although the number of cases is set statistically, it may not be possible to accurately evaluate the causal relationship.

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Author Contributions

SH, NW, and HOni: the conception and design of the research and writing the paper. HK: contributed to the background and discussion check. All authors read and approved the final manuscript.

Ethics and Dissemination

Written informed consent from all the patients screened will be obtained before the procedures start. The study protocol has been approved by Okayama University Certified Review Board (approval number. CRB21-003) and registered in Japan Registry of Clinical Trial (https://jrct.niph.go.jp/), and its registration number is jRCT1061210015. Monitoring and auditing will be carried out throughout the trial. This study was started in June 2021.

Patient and Public Involvement

Patients and/or the public is not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient Consent for Publication

Not required.

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