Cohort study exploring the effect of lenvatinib on differentiated thyroid cancer

Makoto Tahara¹, Hiroshi Takami², Yasuhiro Ito³, Kiminori Sugino⁴, Shunji Takahashi⁵, Hiroshi Takeyama⁶, Hidemitsu Tsutsui⁷, Hisato Hara⁸, Ayako Mitsuma⁹, Hiroyuki Yamashita¹⁰, Takahiro Okamoto¹¹, Iwao Sugitani¹², Yasuo Ohashi¹³ and Tsuneo Imai¹⁴

¹) Department of Head and Neck Cancer Oncology, National Cancer Center Hospital East, Kashiwa, Chiba 277-8577, Japan
²) Department of Surgery, Ito Hospital, Shibuya-ku, Tokyo 150-8308, Japan
³) Department of Clinical Trial, Department of Surgery, Kuma Hospital, Kobe, Hyogo 650-0011, Japan
⁴) Department of Surgery, Ito Hospital, Shibuya-ku, Tokyo 150-8308, Japan
⁵) Department of Medical Oncology, Cancer Institute Hospital of the Japanese Foundation for Cancer Research, 3-8-31, Ariake, Koto-ku, Tokyo 135-8550, Japan
⁶) Department of Breast and Endocrine Surgery, The Jikei University School of Medicine, Minato-ku, Tokyo 105-8461, Japan
⁷) Department of Thoracic and Thyroid Surgery, Tokyo Medical University, Shinjuku-ku, Tokyo 160-0023, Japan
⁸) Department of Breast and Endocrine Surgery, Faculty of Medicine, University of Tsukuba, Tsukuba, Ibaraki 305-8576, Japan
⁹) Department of Clinical Oncology and Chemotherapy, Nagoya University Hospital, Nagoya, Aichi 466-8560, Japan
¹⁰) Department of Surgery, Yamashita Thyroid Hospital, Fukuoka 812-0034, Japan
¹¹) Department of Breast and Endocrine Surgery, Tokyo Women’s Medical University Hospital, Shinjuku-ku, Tokyo 162-8666, Japan
¹²) Department of Endocrine Surgery, Nippon Medical School Graduate School of Medicine, Bunkyo-ku, Tokyo 113-8603, Japan
¹³) Department of Integrated Science and Engineering for Sustainable Society, Chuo University, Bunkyo-ku, Tokyo 112-8551, Japan
¹⁴) National Hospital Organization, Higashinagoya National Hospital, Nagoya, Aichi 465-8620, Japan

Abstract. Lenvatinib is a molecular-targeting agent that was recently approved in Japan for treatment of curatively unresectable, radioactive iodine-refractory, progressive differentiated thyroid cancer (DTC). Because only a few Japanese patients have received lenvatinib in clinical trials, there are limited domestic data on its safety and efficacy or prognostic factors. Therefore, a prospective observational study has been designed to collect safety and efficacy data in at least 300 patients with curatively unresectable DTC receiving lenvatinib therapy (24 mg/day), in order to find predictors of antitumor activity and survival. Patients with progressive curatively unresectable DTC refractory to radioiodine therapy will be enrolled and the primary endpoint will be overall survival. This study is designed to estimate the 95% confidence intervals of the 1-year and 2-year survival rates with a two-sided width of less than 10%. Secondary endpoints will be the time to treatment failure, time to strategy failure, progression-free survival time with clinical progressive disease, response rate, quality of life, safety, and patient reports. The ultimate goal is to obtain information for developing evidence-based guidelines for treatment of DTC, including recommendations on patient selection, dosages, and duration of treatment. This study has been registered with the UMIN Clinical Trials Registry (UMIN000022243).

Key words: Differentiated thyroid cancer, Lenvatinib, Molecular-targeting therapy, Multikinase inhibitor, Radioactive iodine refractory

Overview

In recent years, development of molecular-targeting agents has led to new treatments for various refractory malignancies, but approval of these agents tends to be delayed in Japan and we often have insufficient clinical
Introduction

DTC is initially treated by surgical resection. Patients may subsequently receive radioactive iodine (RAI) to destroy residual normal thyroid tissue and subclinical micrometastases, or to treat recurrent or metastatic disease. If recurrent or metastatic DTC does not respond to RAI therapy, further treatment options are limited and the prognosis is poor [1].

However, placebo-controlled global phase III studies have shown significant improvement of progression-free survival (PFS) by molecular-targeting agents such as sorafenib and lenvatinib in patients with RAI-refractory DTC (RR-DTC) and both agents have become available to treat this tumor, for which there used to be no effective therapy [2-4]. Lenvatinib selectively inhibits multiple receptor tyrosine kinases associated with tumor angiogenesis and/or tumor progression [4, 5].

A randomized, double-blind, phase III study compared lenvatinib (n = 261) versus placebo (n = 131) in patients with RR-DTC [2], revealing significantly better results with lenvatinib than placebo for median PFS (18.3 vs. 3.6 months; p < 0.001) and the overall response rate (64.8% vs. 1.5%; p < 0.001).

Subanalysis of Japanese patients from this study (lenvatinib, n = 30; placebo, n = 10) showed that dose reduction was more frequent among them than in the overall patient population (90.0% vs. 67.8%) and suspension of therapy due to adverse events (AEs) was also more frequent (Japanese, 82.4%; overall, 80.0%) [6]. In addition, a phase II study of lenvatinib in 51 Japanese patients with thyroid cancer (25 with RR-DTC, 9 with medullary carcinoma, and 17 with anaplastic carcinoma) revealed responses of all tumor subtypes and tumor shrinkage in most patients [7].

However, previous studies have provided little evidence about the safety and efficacy of long-term lenvatinib therapy in Japanese patients, including no information about the relation between time to treatment failure (TTF) and the prognosis, the factors influencing TTF, and the effect of clinical characteristics such as the tumor histology and prior therapy.

Objectives

Against this background, a prospective observational study was designed to collect safety and efficacy data on lenvatinib in Japanese patients with curatively unresectable, RAI-refractory, and progressive DTC, in order to find predictors of antitumor activity and survival. The final objective is to provide reference information for developing evidence-based DTC treatment guidelines, including recommendations on patient selection, dosages, and treatment duration.

The most important clinical endpoint of molecular-targeting therapy is survival. Therefore, the primary endpoint of this study will be overall survival (OS), in order to determine whether achieving longer disease control with lenvatinib improves the prognosis. Clinical progressive disease [8] is defined as disease progression with progressive symptoms, multiple disease progression, or life-threatening organ metastasis, and this concept will be used to evaluate tumor progression (first time for thyroid cancer in Japan). This study will also examine quality of life (QOL) due to the relatively long survival of DTC patients.

When lenvatinib is administered, AEs may lead to dose reduction and suspension or discontinuation of therapy. Therefore, we will attempt to elucidate the TTF of lenvatinib and TTF-related factors in actual clinical practice. The rationale for selecting lenvatinib will be investigated along with its influence on the prognosis.

Protocol Digest

Study design

A prospective observational study will enroll patients with curatively unresectable RAI-refractory and progressive DTC who meet the eligibility criteria and are administered lenvatinib in the real-world clinical setting. We will collect information on prognostic factors, including previous treatment, other concomitant therapies, and readministration of lenvatinib after the study period, and we will comprehensively evaluate the utility of this drug.

Lenvatinib administration

Lenvatinib will be administered orally at a dose of 24 mg daily. The dose will be reduced if necessary, depending on the patient’s condition.

Investigations

AEs will be assessed and hematology tests and bio-
chemistry tests will be performed before the start of lenvatinib therapy and in Weeks 4, 12, 26, and 52 of treatment.

Patient-reported compliance, blood pressure, and symptoms
Patients will be asked to keep a diary of treatment compliance and blood pressure measurements during the treatment period up to Week 52. Patients will also be asked to note symptoms such as decreased appetite and fatigue.

QOL survey
QOL will be investigated at baseline and in Weeks 4, 12, 26 and 52 of lenvatinib therapy. The EQ-5D-5L Questionnaire [9] will be employed, which is a common standardized questionnaire for measurement of self-reported health and functioning. Investigators and patients will both answer the questionnaire. The results will also provide data for assessing medical economics.

Antitumor activity
The response to lenvatinib will be assessed at each study site. Assessment of progression will be done according to clinical progressive disease criteria at baseline and in Weeks 4, 12, 26 and 52 of lenvatinib therapy.

All patient survey
At two years (24 months) after the day when the last patient enrolled starts treatment, the outcome, antitumor effect, compliance with lenvatinib therapy, and serious AEs will be investigated in patients who are confirmed to have survived for 52 weeks from initiation of treatment.

Endpoints
The primary endpoint will be OS. The secondary endpoints will be as follows: (1) TTF; (2) time to failure of strategy; (3) PFS time with clinical progressive disease; (4) response rate; (5) QOL survey; (6) safety; and (7) patient reports.

Eligibility criteria
Inclusion criteria will be (1) patients with curatively unresectable, RAI-refractory, and progressive DTC who are suitable for treatment with lenvatinib; (2) patients commencing lenvatinib treatment after this study has been reviewed by the study site committee (e.g., institutional review board or ethical review board); and (3) patients who give informed consent to participation in this study.

Exclusion criteria
Patients who are deemed unsuitable for this study by the attending physician will be excluded.

Sample size
A total of 300 patients will be enrolled in this study at 100 Japanese institutions.

Study period
Patient enrollment will be carried out from the date of review committee approval up to December 2017. The overall study period will be from the date of review committee approval until June 2020.

Statistical considerations
The study is designed to estimate the 95% confidence intervals of the 1-year and 2-year survival rates with a two-sided width of less than 10%. The planned sample size \( n = 300 \) or more was set by calculating the sample sizes required for the above assessment (1-year survival: \( n = 240-370 \); 2-year survival: \( n = 380-590 \) based on data from Study 303 (1-year survival: 81.6%; 2-year survival: 58.2%) with normal approximation of the binomial distribution.

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Registration
The study protocol was registered with the University Hospital Medical Information Network Clinical Trials Registry (UMIN-CTR; UMIN000022243) on 26 May 2016.
Ethical Matters

All of the researchers will conduct this study in compliance with the Declaration of Helsinki and the ethical guidelines for medical research on human subjects [10, 11]. This study has been approved by the institutional review boards of individual participating facilities. Informed consent will be obtained from all patients prior to their participation in the study.

Disclosures

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