BRIEF REPORT

A Phase II Study of Trastuzumab Emtansine in HER2-Positive Non–Small Cell Lung Cancer

Katsuyuki Hotta, MD, PhD, MPH,[a,b,*] Keisuke Aoe, MD, PhD,[c] Toshiyuki Kozuki, MD, PhD,[d] Kadoaki Ohashi, MD, PhD,[a] Kiichiro Ninomiya, MD,[a] Eiki Ichihara, MD, PhD,[a] Toshio Kubo, MD, PhD,[a] Takashi Ninomiya, MD, PhD,[a] Kenichi Chikamori, MD, PhD,[c] Daijiro Harada, MD, PhD,[d] Naoyuki Nogami, MD, PhD,[d] Taizo Hirata, MD, PhD,[a] Shiro Hinotsu, MD, PhD,[b] Shinichi Toyooka, MD, PhD,[e] Katsuyuki Kiura, MD, PhD[a]

[a]*Department of Respiratory Medicine, Okayama University Hospital, Okayama, Japan*
[b]*Center of Innovative Clinical Medicine, Okayama University Hospital, Okayama, Japan*
[c]*Department of Medical Oncology, National Hospital Organization Yamaguchi-Ube Medical Center, Ube, Japan*
[d]*Department of Thoracic Oncology, National Hospital Organization Shikoku Cancer Center, Matsuyama, Japan*
[e]*General Thoracic Surgery and Breast and Endocrinological Surgery, Okayama University Graduate School of Medicine, Okayama, Japan*

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ABSTRACT

Trastuzumab emtansine (T-DM1), an anti–erb-b2 receptor tyrosine kinase 2 (HER2) antibody-drug conjugate, has been shown to significantly improve survival in HER2-positive breast cancer. We report a phase II trial of T-DM1 monotherapy in relapsed NSCLC with documented HER2 positivity (an immunohistochemistry [IHC] score of 3+, both an IHC score of 2+ and fluorescence in situ hybridization positivity, or exon 20 mutation). This study was terminated early because of limited efficacy. The demographic characteristics in the 15 assessable patients were as follows: median age, 67 years; male sex, 47%; performance status of 0 to 1, 80%; HER2 status IHC 3+, 33%; HER status IHC 2+/fluorescence in situ hybridization–positive, 20%; and exon 20 mutation, 47%. The median number of delivered cycles was 3 (range 1–11). One patient achieved a partial response with an objective response rate of 6.7% (90% confidence interval: 0.2–32.0). With a median follow-up time of 9.2 months, the median progression-free survival time and median survival time were 2.0 and 10.9 months, respectively. Grade 3 or 4 adverse events included thrombocytopenia (40%) and hepatotoxicity (20%) without any treatment-related deaths. T-DM1 had a limited efficacy for HER2-positive NSCLC in our cohort. Applying the concept of precision medicine to tumors appears challenging; thus, additional molecular approaches are warranted.

Keywords: Non–small cell lung cancer; HER2; trastuzumab emtansine; precision medicine

Introduction

Recent driver oncogene–based precision therapy has dramatically changed the treatment strategy for NSCLC, representatively targeting *EGFR* and ALK receptor tyrosine kinase gene (*ALK*) aberrations. However, outcomes in other lung cancers remain poor even with standard chemotherapy.[1,2] Consequently, further development of novel oncogenes and corresponding targeted therapeutic agents is warranted.

*Corresponding author.

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Trial Registration: A Study of Trastuzumab Emtansine in Patients with HER2-Positive, Recurrent Metastatic Non-Small Cell Lung Cancer. UMIN000017709.

Address for correspondence: Katsuyuki Hotta, MD, PhD, MPH, Center for Innovative Clinical Medicine, Okayama University Hospital, 2-5-1, Shikata-cho, Okayama 700 8558, Japan. E-mail: khotta@okayama-u.ac.jp

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In addition, erb-b2 receptor tyrosine kinase 2 (HER2) aberrations have been detected, accounting for 4.7% to 10% of NSCLC in terms of grade 3+ HER2 immunohistochemistry (IHC) expression.[3] Additionally, the large epidemiological studies have identified tumors with positive HER2 fluorescence in situ hybridization (FISH) in 1.7% and HER2-mutant tumors in 3.6%.[4]

Trastuzumab emtansine (T-DM1) is a novel antibody-drug conjugate that uses trastuzumab, an anti-HER2 antibody, to deliver the maytansinoid antimicrotubule agent DM1, which binds to microtubules in a manner similar to that of vinca alkaloids.[5] T-DM1 has been shown to confer a survival benefit over the standard regimen applied in HER2-positive, relapsed breast cancer.[6]

As for NSCLC, the Calu 3 lung carcinoma cell line (HER2-IHC 3+) showed preclinically dose-dependent inhibition of cell growth after T-DM1 treatment.[5] Moreover, lung tumors with erb-b2 receptor tyrosine kinase 2 gene (*HER2*) insertion mutations in exon 20, a confirmed driver oncogene, showed dramatic shrinkage with HER2-targeted therapy.[7] These studies suggested that T-DM1 might be effective against both HER2-positive lung and breast cancers.

However, few prospective studies of HER2-targeted therapy for lung cancer have been conducted, prompting us to launch this phase II trial.

Methods

Study Population and Intervention

Patients who met the eligibility criteria, including HER2 positivity,[8] were enrolled for registration at three institutes in Japan: Yamaguchi-Ube Medical Centre, Shikoku Cancer Centre, and Okayama University Hospital. T-DM1 was kindly provided by Chugai Pharmaceuticals. Patients had to have had one or more lines of prior chemotherapy. Written informed consent was obtained from all patients before applying the study procedures. This study was approved by the institutional review boards.

Patients received T-DM1 intravenously, at a dose of 3.6 mg/kg over 90 minutes on day 1 of each 21-day cycle until the disease progressed or unmanageable toxic effects developed, as similar to the protocol for breast cancer.[6]

HER2 Tests

HER2 status was assessed in the laboratory (SRL, Tokyo, Japan) by using tumor formalin-fixed, paraffin-embedded archived tissues; no cytologic specimens were allowed, but biopsy or surgical specimens were. The level of HER2 protein expression was determined by IHC by using the Ventana I-VIEW PATHWAY anti–HER-2/neu (4B5) (Roche, Basel, Switzerland).[9] IHC scores of 3+ and 2+ were considered strongly and weakly positive, respectively.[9] FISH assays were also performed using the PathVysion HER-2 DNA probe kit (Vysis/Abbott Laboratories, Downers Grove, IL) to ascertain negativity or positivity according to a cutoff value of 2.0 (of the median ratio of HER2 to chromosome 17 copy numbers). We conducted a separate validation study to review the IHC and FISH specimens to define their positivity (unpublished data, Hotta K, 2017). Mutation analysis was performed by direct sequencing at a central laboratory (Genetic Labo, Japan) to detect known mutations (M774_A775insAYVM, A775_G776insYVMA, G776L insC, G776V insC, and P780_Y781insGSP).[4]

Finally, in this trial, HER2 was defined as positive in the presence of an IHC score of 3+, an IHC score of 2+ and FISH positivity, or an exon 20 insertion mutation.

Statistical Analysis

The primary end point was the objective response rate (ORR), which was centrally confirmed by three independent board members with the Response Evaluation Criteria in Solid Tumors (version 1.1) every 6 weeks. Secondary outcome end points included safety, overall survival, and progression-free survival (PFS). We considered the lower limit of interest to be 10%.[10] Assuming that a 20% or more increase in historical data in ORR would be clinically meaningful, we needed 30 patients with a one-sided α of 0.05 and 1-β of 0.8, considering a 10% dropout rate, according to the Simon minimax design. We also planned to conduct an interim analysis after the first 15 patients had been registered; early study termination would be considered if the ORR was obtained in no more than one patient. The confidence interval (CI) of the ORR was calculated with a confidence coefficient of two-tailed 90% and 95%.

Regarding the efficacy analysis, waterfall and swimmer plots were also produced. The PFS and overall survival times were calculated from the date of registration to the first documented date of disease progression and date of death, respectively, by the Kaplan-Meier method. Statistical analyses were conducted with STATA software (version 14.0, StataCorp LP, College Station, TX).

Results

Patients

This study was terminated early because of the limited efficacy, which did not satisfy the criteria in the interim analysis; this led to only 16 of the 30 patients planned being registered between September 2015 and November 2016. Among them, 15 were considered assessable for further analysis: one patient was excluded because of a protocol deviation in the registration process. The patients' characteristics are listed in Table 1. Regarding HER2 status, 33% of cases were scored IHC 3+, 20% were scored IHC 2+/FISH positive, and 47% showed the