A Phase II Study of Gefitinib With Concurrent Thoracic Radiotherapy in Patients With Unresectable, Stage III Non–small-cell Lung Cancer Harboring EGFR Mutations (WJOG6911L)

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Abstract

Locally advanced non–small-cell lung cancer (NSCLC) is curable. Standard treatment is concurrent chemoradiotherapy, but its efficacy with cytotoxic agents seems to reach a plateau. Among patients with advanced NSCLC who have epidermal growth factor receptor (*EGFR*) mutation, *EGFR*-tyrosine kinase inhibitor is the key drug. Thus, a similar strategy should be tested in patients with locally advanced NSCLC who have *EGFR* mutation. This single arm, phase II study aims to explore the efficacy and tolerability of gefitinib with concurrent thoracic radiotherapy in patients with unresectable stage III NSCLC harboring *EGFR* mutations. The primary endpoint is progression-free survival rate at 2 years. The secondary endpoints are overall response rate, progression-free survival, overall survival, and safety. A total of 27 patients will be enrolled in this trial.

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Introduction

Locally advanced non–small-cell lung cancer (LA-NSCLC) is a curable disease, and the standard treatment is concurrent chemoradiotherapy (CRT). Although newer cytotoxic agents have been tested, their efficacy results seem to reach a plateau.[1] Another strategy to improve treatment outcome is to introduce novel agents, like molecular targeted drugs or immune-checkpoint inhibitors. Recently, the programmed death ligand-1 inhibitor, durvalumab, significantly prolonged progression-free survival (PFS) among patients with LA-NSCLC who responded to CRT in a phase III PACIFIC trial.[2] However, its subset analysis showed that epidermal growth factor receptor *(EGFR)*-mutated patients did not benefit from durvalumab. Retrospective studies suggest that about 30% of patients with LA-NSCLC have *EGFR* mutation.[3,4] Another regimen should thus be developed for this population.

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Among patients with NSCLC who have sensitive *EGFR* mutation, EGFR-tyrosine kinase inhibitor (TKI) is the key drug.[5,6] Overall response rate (ORR) with EGFR-TKI is about double that of platinum-doublet chemotherapy. In addition, a preclinical study suggested that gefitinib had a radio-sensitizing effect.[7] These rationales suggest that EGFR-TKI plus thoracic radiotherapy should be tested for *EGFR*-mutated LA-NSCLC. Several studies using gefitinib monotherapy combined with thoracic radiotherapy have been conducted, but all of them allowed participation of both *EGFR*-mutated and wild-type patients. In one study, 2 of 3 patients who lived more than 5 years after gefitinib plus thoracic radiotherapy were later proved to harbor the *EGFR* mutation.[8] Another study showed the feasibility of gefitinib plus concurrent thoracic radiotherapy where the incidence of interstitial lung disease was about 2.9%.[9] This was comparable to that with gefitinib monotherapy in Japanese patients with *EGFR*-mutated NSCLC.[10]

Based on this information, we planned a phase II study of gefitinib with concurrent thoracic radiotherapy in patients with unresectable, stage III NSCLC harboring *EGFR* mutations (WJOG6911L). Here, we introduce the details of this study.

Protocol of Study WJOG6911L

Objectives

This study aims to explore the efficacy and the tolerability of gefitinib with concurrent thoracic radiotherapy in patients with unresectable, stage III NSCLC harboring *EGFR* mutations.

Study Design

This is a single-arm, prospective phase II study. An overview is shown in Figure 1.

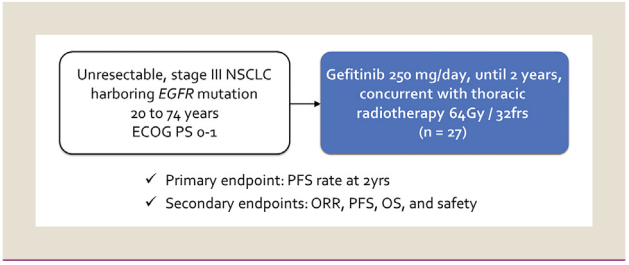
Endpoints

The primary endpoint is set as the PFS rate at 2 years according to the Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1. Secondary endpoints are ORR, PFS, overall survival, and safety.

Eligibility Criteria

Inclusion Criteria. Patients must fulfill all the following criteria: (1) Pathologically confirmed NSCLC; (2) Treatment-naive, unresectable stage III disease. Patients with T3N1 disease, contralateral mediastinal lymph node metastasis, pulmonary metastasis, and atelectasis of the entire hemithorax are excluded; (3) Harboring *EGFR* mutation (*exon 19 deletion, or exon 21 L858R point mutation*); (4) Age 20 to 74 years; (5) Eastern Cooperative Oncology Group performance status of 0 to 1; (6) Evaluable target lesions as per RECIST v 1.1; (7) Adequate organ function; (8) Confirmed as eligible for the protocol defined radiotherapy by radiologists; and (9) Written informed consent provided.

Figure 1 Study Overview



Abbreviations: ECOG PS = Eastern Cooperative Oncology Group performance status; EFGR = epidermal growth factor receptor; frs = fractions; ORR = overall response rate; OS = overall survival; PFS = progression-free survival.

Exclusion Criteria. Patients are excluded from the study if they meet any of the following criteria: (1) Harboring *EGFR exon 20 T790M* mutation; (2) Incapable of oral intake; (3) Intestinal paralysis or ileus; (4) Chronic diarrhea; (5) Exhibiting significant interstitial pneumonitis, or pulmonary fibrosis in chest computed tomography (CT); (6) Active infection; (7) Positive for hepatitis B virus antigen; (8) Uncontrolled diabetes mellitus; (9) Severe heart disease; (10) Systemic treatment with steroids; (11) Concomitant cancers within 5 years; (12) History of thoracic radiotherapy; (13) History of serious drug allergy; (14) Confirmed or possible pregnancy, currently breast feeding; and (15) Other conditions deeming the patient unsuitable for this study.

Treatment

Treatment consists of gefitinib monotherapy plus concurrent thoracic radiotherapy. An oral dose of 250 mg of gefitinib is administered daily beginning on day 1, for 2 years. Thoracic radiotherapy is also be started on day 1 and delivered 5 days per week in 2-Gy fractions to a total dose of 64 Gy. Before registration, positron emission tomography-computed tomography (PET-CT) must be taken, and 3-dimensional CT planning is mandatory. Involved-field radiotherapy is adopted in this study to avoid the risk of gefitinib-induced interstitial pneumonia. Gross tumor volume consists of the primary tumor and clinically positive lymph nodes seen either on the planning CT (>1 cm short axis diameter) or pretreatment PET scan. The clinical target volume includes gross tumor volume plus a total margin of at least 0.5 cm. The total planning target volume includes the clinical target volume plus a total margin of at least 0.5 cm. The dose was prescribed at a reference point. The planning target volume is encouraged to cover 95% to 107% of prescribed dose. All doses of radiation are calculated with inhomogeneity corrections (superposition/convolution dose calculation algorithms). The maximum spinal cord dose is limited to 52 Gy, and 1 cc of spinal cord should not exceed 48 Gy. The volume of both lungs that receive $\geq$ 20 Gy (V20) should not exceed 35% of the total. Brachial plexus doses should be kept below 66 Gy.

RT Quality Assurance Review

For the radiotherapy quality assurance review, we collected the Digital Imaging and Communications in Medicine data of the pretreatment diagnostic chest radiographs; CT and PET-CT; CT planning and portal images; radiotherapy planning data including dose distribution, structures, and plan summaries; and radiotherapy charts of all patients.

Follow-up and Assessment

To assess the efficacy, chest CT is taken every 2 months for the first 6 months, and every 6 months after that. Brain magnetic

resonance imaging is taken once a year. Adverse events are graded using the Common Terminology Criteria for Adverse Events, version 4.0.

Statistical Analysis

We previously reported that the PFS rate at 2 years could be a reliable surrogate maker for the 5-year survival rate in patients with LA-NSCLC.[11] Thus, the PFS rate at 2 years is set as the primary endpoint of this study. Based on the Kaplan-Meier curve of PFS in the pivotal study of CRT,[12] we assumed an improved PFS rate at 2 years from 20% to 40%. Twenty-five eligible patients were required to ensure a statistical power of 0.75 at a 1-sided score test with an alpha error of 0.05. Assuming that around 5% ineligibles will be identified after the recruitment, 27 patients are recruited.

Ethical Considerations

The study is conducted in compliance with the principles of the Declaration of Helsinki. The protocol was approved by the institutional review board of each participating institution. Written informed consent is obtained from all patients before any screening or inclusion procedures. This protocol was registered at the website of University Hospital Medical Information Network, Japan (protocol identification no. UMIN000008366).

Discussion and Conclusion

Among patients with metastatic NSCLC with oncogenic driver mutations, molecular targeted drugs have dramatically changed the standard treatment. Therefore, introduction of these agents into treatment for LA-NSCLC seems to be a reasonable approach. Several studies to test the utility of EGFR-TKI concurrent with radiotherapy did not show significant results, mainly owing to patient selection. This study is the first to explore the efficacy and tolerability of gefitinib monotherapy concurrent with radiotherapy in *EGFR*-mutated, unresectable LA-NSCLC. We believe that the results of this study will impact on the future strategy toward this population.

Participating Institutions

Participating institutions are as follows: Shizuoka Cancer Center, Toyama University, Izumi Municipal Hospital, Kyoto University, Tokyo Metropolitan Center and Infectious Disease Center Komagome Hospital, National Hospital Organization Disaster Medical Center, Kindai University, Osaka City General Hospital, Hyogo Cancer Center, Juntendo University, Osaka City Medical University, Hiroshima City Hiroshima Citizens Hospital, Kanagawa Cancer Center, Kishiwada City Hospital, Kansai Medical University, Kurume University, Aichi Cancer Center, The Cancer Institute Hospital of JFCR, Hokkaido University, Kitazato University, Wakayama Medical University, Hiratsuka City Hospital, Niigata Cancer Center Hospital and National Cancer Center Hospital East.

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Disclosures

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References

1. Senan S, Brade A, Wang LH, et al. PROCLAIM: randomized phase III trial of pemetrexed-cisplatin or etoposide-cisplatin plus thoracic radiation therapy followed by consolidation chemotherapy in locally advanced nonsquamous non-small-cell lung cancer. *J Clin Oncol* 2016; 34:953-62.
2. Antonia SJ, Villegas A, Daniel D, et al. Durvalumab after chemoradiotherapy in stage III non-small-cell lung cancer. *N Engl J Med* 2017; 377:1919-29.
3. Akamatsu H, Kaira K, Murakami H, et al. The impact of clinical outcomes according to *EGFR* mutation status in patients with locally advanced lung adenocarcinoma who received concurrent chemoradiotherapy. *Am J Clin Oncol* 2014; 37:144-7.
4. Hayashi H, Okamoto I, Kimura H, et al. Clinical outcomes of thoracic radiotherapy for locally advanced NSCLC with *EGFR* mutations or EML4-ALK rearrangement. *Anticancer Res* 2012; 32:4533-7.
5. Mitsudomi T, Morita S, Yatabe Y, et al. Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): an open label, randomised phase 3 trial. *Lancet Oncol* 2010; 11:121-8.
6. Maemondo M, Inoue A, Kobayashi K, et al. Gefitinib or chemotherapy for non-small-cell lung cancer with mutated *EGFR*. *N Engl J Med* 2010; 362:2380-8.
7. Williams KJ, Telfer BA, Stratford IJ, et al. ZD1839 ('Iressa'), a specific oral epidermal growth factor receptor-tyrosine kinase inhibitor, potentiates radiotherapy in a human colorectal cancer xenograft model. *Br J Cancer* 2002; 86:1157-61.
8. Okamoto I, Takahashi T, Okamoto H, et al. Single-agent gefitinib with concurrent radiotherapy for locally advanced non-small cell lung cancer harboring mutations of the epidermal growth factor receptor. *Lung Cancer* 2011; 72:199-204.
9. Niho S, Ohe Y, Ishikura S, et al. Induction chemotherapy followed by gefitinib and concurrent thoracic radiotherapy for unresectable locally advanced adenocarcinoma of the lung: a multicenter feasibility study (JCOG 0402). *Ann Oncol* 2012; 23:2253-8.
10. Akamatsu H, Inoue A, Mitsudomi T, et al. Interstitial lung disease associated with gefitinib in Japanese patients with *EGFR*-mutated non-small-cell lung cancer: combined analysis of two Phase III trials (NEJ 002 and WJTOG 3405). *Jpn J Clin Oncol* 2013; 43:664-8.
11. Akamatsu H, Mori K, Naito T, et al. Progression-free survival at 2 years is a reliable surrogate marker for the 5-year survival rate in patients with locally advanced non-small cell lung cancer treated with chemoradiotherapy. *BMC Cancer* 2014; 14:18.
12. Yamamoto N, Nakagawa K, Nishimura Y, et al. Phase III study comparing second- and third-generation regimens with concurrent thoracic radiotherapy in patients with unresectable stage III non−small-cell lung cancer: West Japan Thoracic Oncology Group WJTOG0105. *J Clin Oncol* 2010; 28:3739-45.