A prospective Phase II trial of low-dose afatinib for patients with EGFR, mutation-positive, non-small lung cancer (TORG1632)

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BACKGROUND

In the subgroup analysis of the LUX Lung 3 study, patients who were leading a dose-reduction trend occurred in 76% of afatinib-treated Japanese patients. The most common adverse events leading to a dose reduction of afatinib were rash/acne (65%), nausea (46%), and diarrhoea (30%).

A hitatinib is an effective treatment option for patients with epithelial growth factor receptor (EGFR) mutation-positive non-small lung cancer (NSCLC). However, it frequently causes dose modifications.

During the use of the drug, there were 3 kinds of bleeding modalities. 
- Treatment was continued until disease progression, unacceptable toxicity, or the withdrawal of consent.
- When the patients had drug resistance, the drug was discontinued. 
- If patients had grade 3 or higher adverse events, the drug was discontinued.

RESULTS

From March 2017 through September 2018, patients were enrolled from 21 institutions in Japan. The median age was 70 years (range, 37–86), and 26 patients (52.8%) were male. After a median follow-up of 19 months (5.8–100 months) and EGFR point mutation (43.4%). Most patients had a performance status of 0 or 1 (88.8%).

Table 1 Patients characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Median (Q1-Q3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>70 (58-75)</td>
</tr>
<tr>
<td>Gender</td>
<td>Female 53 (52.8%)</td>
</tr>
<tr>
<td>Smoking history</td>
<td>Yes 33 (62.3%)</td>
</tr>
<tr>
<td>PS</td>
<td>0 26 (49.1%)</td>
</tr>
</tbody>
</table>
| EGFR status | L858 Exon19 53 (100%)
| EGFR point mutation | Yes 26 (49.1%) |
| EGFR activating mutation | Yes 26 (49.1%) |
| EGFR point mutation (L858R, Exon 19) | No 17 (32.1%) |
| Histology | Adenocarcinoma 53 (100%)
| Histology | Squamous cell cancer 24 (45.3%)
| Histology | Other 1 2 (3.8%)
| Histology | SCLC 0 0 (0.0%)
| Histology | Metastatic 1 2 (3.8%)

Efficacy

Whenever the dose of afatinib was escalated to a maximum dose per day of 30 mg, a disease control rate of 76% was achieved. The most common adverse events leading to a dose reduction of afatinib were rash/acne (65%), nausea (46%), and diarrhoea (30%).

Table 2 Tumor response

<table>
<thead>
<tr>
<th>Variable</th>
<th>Median (Q1-Q3)</th>
</tr>
</thead>
</table>
| Tumor response | CR 0 0%
| Tumor response | PR 0 0%
| Tumor response | SD (growing) 31 (56.6%)
| Tumor response | SD (not growing) 22 (41.5%)
| Tumor response | PD 0 0%

Table 3 Multivariate analyses of progression-free survival

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
</table>
| Gender | 1.39 (0.86-2.10)
| Age (y) | 0.97 (0.96-0.98)
| PS | 0.65 (0.35-1.23)
| Smoking history | 1.28 (0.70-2.33)

Table 4 Multivariate analyses of overall survival

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
</table>
| Gender | 1.26 (0.72-2.21)
| Age (y) | 0.96 (0.94-0.99)
| PS | 0.71 (0.41-1.22)
| Smoking history | 0.95 (0.57-1.58)

STUDY OBJECTIVES

- To evaluate the clinical efficacy and tolerability of low-dose 20 mg daily of afatinib for treatment-naive patients with advanced NSCLC with EGFR mutation-positive.
- To determine the optimal dose of afatinib in this setting.

PATIENTS AND METHODS

This study was a multicenter, open-label, phase II trial (UMIN000027736).

Patients were included if they were ≥20 y of age, had histologically confirmed non-small-cell lung cancer (NSCLC) with a common activating EGFR mutation (L858R or Exon 19 deletion), and an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0–1.

Inclusion criteria

- Patients with NSCLC with a common activating EGFR mutation (L858R or Exon 19 deletion).
- Patients who are ≥20 years of age and have an ECOG PS of 0–1.

Exclusion criteria

- Patients with a history of other malignancies, except for basal cell carcinoma and squamous cell carcinoma of the skin.
- Patients who are pregnant or lactating.
- Patients who have active interstitial lung disease or active pneumonitis.
- Patients who are receiving other investigational agents.

Dose reduction criteria and discontinuation criteria

- The dose of afatinib was reduced to 15 mg daily, if the patient developed grade 3 or higher adverse events requiring treatment that would be considered as one of standard therapy for EGFR mutation-positive NSCLC.

Adverse event and clinical outcome

- All adverse events were classified using the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0).
- Adverse events were assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0).

Additional study

- Eight of 19 patients (42.1%) including 4 patients (21.1%) with different EGFR mutation-positive NSCLC.
- On the basis of the median follow-up of 19 months, the number of patients required to provide an 80% probability of survival at 2 years was 20 (95% CI: 10–36) with a 1-sided alpha level of 0.05 and a beta level of 0.20.
- A total of 19 patients with different EGFR mutation-positive NSCLC.

CONCLUSION

- Adverse events (AEs) of grade 3 or higher occurred in 12 patients (22.5%) including diarrhea (4 patients, 21.1%) and grade 4 was observed in 2 patients (10.5%).
- Blood test results often change dose modifications.

Because low-dose afatinib from a pharmacokinetic and pharmacodynamic perspective, low-dose afatinib would be considered as one of standard therapy for EGFR mutation-positive NSCLC by demonstrative clinical outcome and tolerability.