Quality of life and disease-related symptoms in previously treated Japanese patients with non-small-cell lung cancer: results of a randomized phase III study (V-15-32) of gefitinib versus docetaxel


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Background: This report describes quality of life (QoL) findings of a randomized study comparing gefitinib with docetaxel in patients with advanced/metastatic pretreated non-small-cell lung cancer.

Patients and methods: This open-label, phase III study randomized 490 Japanese patients to gefitinib (250 mg/day) or docetaxel (60 mg/m2/3 weeks), with survival as the primary outcome. Preplanned QoL analyses included Functional Assessment of Cancer Therapy-Lung (FACT-L), Trial Outcome Index (TOI) and Lung Cancer Subscale (LCS) improvement rates, and mean change from baseline.

Results: Gefitinib showed statistically significant benefits over docetaxel in QoL improvement rates (FACT-L 23% versus 14%, P = 0.023; TOI 21% versus 9%, P = 0.002) and mean change from baseline score [mean treatment difference: FACT-L 3.72 points, 95% confidence interval (CI) 0.55–6.89, P = 0.022; TOI 4.31 points, 95% CI 2.13–6.49, P < 0.001], although differences did not meet the clinically relevant six-point change. There were no significant differences between treatments in LCS improvement rates (23% versus 20%, P = 0.562) or mean change from baseline score (0.63 points, 95% CI −0.07 to 1.34, P = 0.077).

Conclusions: Gefitinib improved aspects of QoL over docetaxel, with superior objective response rate and a more favorable tolerability profile and no statistically significant difference in overall survival (although noninferiority was not statistically proven).

Key words: docetaxel, gefitinib, non-small-cell lung cancer, quality of life

Introduction

Docetaxel is an established treatment of patients with previously treated advanced non-small-cell lung cancer (NSCLC) worldwide, including Japan; however, this is associated with typical cytotoxic side-effects including hematological toxicity, especially grade 3/4 neutropenia [1, 2]. Alternative agents with an improved tolerability profile, such as the epidermal growth factor receptor tyrosine kinase inhibitor (EGFR TKI) gefitinib, have been investigated in this setting [3–5].

In this randomized phase III study (V-15-32) comparing gefitinib versus docetaxel in previously treated Japanese patients with NSCLC, the primary objective (noninferiority of gefitinib versus docetaxel) was not statistically proven for overall survival (OS) [hazard ratio (HR) 1.12, 95.24% confidence interval (CI) 0.89–1.40], according to the predefined noninferiority criterion (upper CI for HR < 1.25) [6]. However, there were no statistically significant differences in OS (P = 0.330) or progression-free survival (PFS; P = 0.335) and gefitinib had a superior objective response rate (ORR) and a more favorable tolerability profile than docetaxel. Because of the significant...
patients and methods

study design

This phase III study compared the effects of gefitinib versus docetaxel in Japanese patients with advanced/metastatic (stage IIIb/IV) or recurrent NSCLC who failed one or two chemotherapy regimens. Details of the study design and eligibility criteria have been published [6]. The primary end point was OS; the study aimed to show noninferiority of gefitinib versus docetaxel. Secondary end points were PFS, time-to-treatment failure, ORR, disease control rate, QoL, disease-related symptoms, safety, and tolerability.

The study was carried out in accordance with the Declaration of Helsinki and the International Conference on Harmonization/Good Clinical Practice (GCP), applicable regulatory requirements, and the AstraZeneca policy on Bioethics. The study protocol was approved by each institutional review board and written informed consent was obtained from all patients.

QoL assessments and analyses

The Functional Assessment of Cancer Therapy-Lung (FACT-L) questionnaire was used to assess QoL at baseline and every 4 weeks during study treatment until week 12. The FACT-L questionnaire is a validated, self-report questionnaire comprising physical, functional, social/family, emotional well-being subscales and Lung Cancer Subscale (LCS) [7]. The Trial Outcome Index (TOI), the sum of the physical, functional subscales, and LCS is reported to be a precise indicator of functional outcomes [7]. Disease-related symptoms were assessed weekly using the LCS. As previously reported [8], clinically relevant improvement was defined as change from baseline of \( +6 \) for FACT-L or TOI or \( +2 \) for LCS, on two visits at least 28 days apart. The assessable for LCS and assessable for QoL populations were subsets of the intent-to-treat (ITT) population with nonmissing baseline and one or more nonmissing post-baseline LCS and QoL assessments, respectively.

Preplanned analyses of FACT-L, TOI, and LCS scores included the following: mean change from baseline and 95% CI of the difference in mean change; mean and best change from baseline for each subscale with two-sample \( t \)-test comparing treatments; mean and best change from baseline for individual questions; and correlation between mean change and best change from baseline and tumor response.

results

patients

Of 245 gefitinib and 244 docetaxel patients (one patient in the docetaxel arm was excluded due to GCP violation) in the ITT population, 185 (76%) and 173 (71%) patients, respectively, were assessable for QoL and 225 (92%) and 211 (86%) patients, respectively, were assessable for LCS. The demographic characteristics of the assessable for QoL and assessable for LCS populations (Supplemental Table 1, available at Annals of Oncology online) were representative of the overall study population [6].

QoL and disease-related symptoms at baseline

The baseline FACT-L, TOI, and LCS scores were similar between treatment groups (Table 1).

compliance and evaluability

Baseline compliance rates [(evaluable questionnaires during the treatment period)/(expected questionnaires) \( \times 100 \)] for gefitinib and docetaxel were high: 92% and 86%, respectively, for FACT-L and 93% and 87%, respectively, for LCS. During the first 12-weeks treatment, compliance rates for gefitinib and docetaxel were between 77% and 89% and 77% and 93%, respectively, for FACT-L completion and between 76% and 98% and 71% and 98%, respectively, for LCS completion, with smaller numbers of patients as time progressed as expected (Supplemental Table 2, available at Annals of Oncology online). Evaluation rates [(evaluable questionnaires during the treatment period)/(received questionnaires) \( \times 100 \)] were also high at between 88% and 100% (Supplemental Table 2, available at Annals of Oncology online).

QoL and symptom improvement

Significantly, more gefitinib-treated patients experienced a clinically relevant improvement in QoL (FACT-L and TOI) compared with docetaxel (Figure 1). There was no evidence of a difference between treatments in terms of symptom improvement rates measured by LCS (Figure 1).

Table 1. Baseline FACT-L, TOI, and LCS scores (assessable population)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Gefitinib</th>
<th>Docetaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( n )</td>
<td>Mean ± SD</td>
</tr>
<tr>
<td>FACT-L</td>
<td>185</td>
<td>98.5 (64.0–100.0)</td>
</tr>
<tr>
<td>TOI</td>
<td>185</td>
<td>58.4 (26.0–84.0)</td>
</tr>
<tr>
<td>LCS</td>
<td>225</td>
<td>19.0 (5.0–28.0)</td>
</tr>
</tbody>
</table>

SD, standard deviation; FACT-L, Functional Assessment of Cancer Therapy-Lung; TOI, Trial Outcome Index; LCS, Lung Cancer Subscale.

Supporting post hoc analyses of FACT-L, TOI, and LCS scores included the following: similar analyses using best change from baseline score instead of mean change; mean and best change from baseline for each subscale with two-sample \( t \)-test comparing treatments; mean and best change from baseline for individual questions; and correlation between mean change and best change from baseline and tumor response.
Time to worsening was significantly longer on gefitinib than docetaxel for TOI, numerically longer for FACT-L, and slightly longer for LCS (Figure 2).

Mean change from baseline for FACT-L, TOI, and LCS at each visit during the first 12 weeks of treatment is shown in Supplemental Figure 1 (available at Annals of Oncology online).
Statistically significant differences between treatments in mean change from baseline for QoL score (FACT-L and TOI) in favor of gefitinib were observed, but the differences did not meet the predefined, clinically relevant six-point change (FACT-L: 3.72 points, 95% CI 0.55–6.89, \( P = 0.022 \); TOI: 4.31 points, 95% CI 2.13–6.49, \( P < 0.001 \)) (Table 2). There was no significant difference between treatments in mean change from baseline for LCS score (0.63 points, 95% CI -0.07 to 1.34, \( P = 0.077 \)) (Table 2).

Post hoc analyses of mean change from baseline in the FACT-L subscales identified significant differences in favor of gefitinib over docetaxel in the physical (\( P = 0.002 \)) and functional well-being subscales (\( P = 0.002 \)) but not in the social/family (\( P = 0.494 \)) or emotional well-being subscales (\( P = 0.663 \)) (Figure 3). In post hoc analyses, individual FACT-L questions with the largest differences between treatments in mean change from baseline (20.3 points difference of absolute value, all favoring gefitinib) were ‘I am bothered by hair loss’ (difference 2.03 points; question not included in calculating FACT-L, TOI, and LCS scores); ‘I am content with the quality of my life right now’ (0.47 points); ‘I am enjoying the things I usually do for fun’ (0.33 points); ‘I am sleeping well’ (0.31 points); and ‘I have a good appetite’ (0.31 points). No question favored docetaxel by >0.21 points (Supplemental Table 3, available at Annals of Oncology online).

The results of post hoc analyses of best change from baseline score were consistent with the preplanned mean change from baseline score analyses.

QoL and symptom improvement by objective tumor response

Mean change from baseline in FACT-L, TOI, and LCS improved as best overall objective tumor response improved for both gefitinib and docetaxel (Supplemental Table 4, available at Annals of Oncology online). There was a higher correlation between changes and tumor response for gefitinib than docetaxel, which may be caused by more disperse distribution of objective tumor response for gefitinib. Similar results with slightly higher correlations were seen using best change from baseline.

**Discussion**

In this randomized phase III study in previously treated advanced NSCLC, noninferiority of gefitinib versus docetaxel was not statistically proven for OS, although there were no statistically significant differences in OS or PFS between treatments. However, gefitinib demonstrated statistically significant benefits over docetaxel in QoL improvement rates and mean change from baseline QoL score (measured by \( P = \)...
FACT-L and TOI) in addition to superior ORR and a more favorable tolerability profile for gefitinib. Post hoc analyses showed that the biggest differences in favor of gefitinib were in the FACT-L physical and functional well-being subscales, the two subscales thought the most responsive to short-term changes [7]. Conversely, there were no significant differences between treatments in symptom improvement rates or mean change from baseline symptom score as measured by the LCS. In line with these results, time to worsening of QoL tended to be longer for gefitinib than docetaxel, significantly so for TOI. Further, post hoc analyses showed that there appeared to be a higher correlation between QoL and symptom changes and objective tumor response with gefitinib compared with docetaxel. Compliance and evaluability rates were high supporting the validity of these QoL data [9].

The QoL benefits seen in this study are consistent with other studies of gefitinib and docetaxel [3, 4, 10–13]. Docetaxel has demonstrated symptom relief including improvements in patient-rated pain scores ($P = 0.005$) and QoL with less deterioration in Lung Cancer Symptom Scale (LCSS) pain score ($P < 0.05$) in pretreated patients with advanced NSCLC compared with best supportive care [11]. Despite an improved tolerability profile with pemetrexed, no improvements were observed in QoL measurements compared with docetaxel in a phase III second-line setting in predominantly Western patients: symptom improvement rates (21% versus 22%, respectively, measured by LCSS) and rates of improvement or stabilization of anorexia (56% versus 61%), fatigue (55% versus 57%), cough (64% versus 64%), dyspnea (64% versus 60%), hemoptysis (70% versus 73%), and pain (64% versus 62%) were similar for pemetrexed and docetaxel [12]. In a phase II study in previously treated patients with advanced NSCLC (SIGN), QoL improvement rate of gefitinib was higher than docetaxel (34% versus 26%) and the mean change from baseline in FACT-L score was similar between the treatments (1.55 versus 0.39, $P = 0.63$) [10]. A larger international phase III study (INTEREST) with a very similar design to V-15-32 but in predominantly Western patients has established noninferior survival of gefitinib versus docetaxel in 1466 patients with pretreated advanced NSCLC [13]. Statistically significant benefits in QoL improvement rates for gefitinib over docetaxel were also observed in this study (FACT-L 25% versus 15%, $P < 0.0001$; TOI 17% versus 10%, $P = 0.0026$), with no significant difference between treatments in symptom improvement rates (LCSS 20% versus 17%, $P = 0.1329$) [13]. Another EGFR TKI, erlotinib, was associated with QoL improvements [using the European Organization for Research and Treatment of Cancer QoL questionnaire (QLQ-C30)] compared with placebo [14] but no comparative data for erlotinib versus docetaxel exist.

In conclusion, gefitinib demonstrated statistically significant QoL benefits compared with docetaxel in the current study. From this study, we believe that treatment with gefitinib remains an effective treatment option with potential QoL advantages for previously treated Japanese patients with locally advanced/metastatic NSCLC.

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