Gefitinib vs. chemotherapy as first-line therapy in advanced non-small cell lung cancer: Meta-analysis of phase III trials

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**ABSTRACT**

**Background:** Gefitinib is an oral tyrosine kinase inhibitor against the epidermal growth factor receptor (EGFR). It has been shown to be active in patients with advanced non-small cell lung cancer (NSCLC) whose tumors contain EGFR mutations.

**Methods:** We performed a meta-analysis of four randomized studies that compared gefitinib with chemotherapy in the first-line treatment of patients with advanced NSCLC: IPASS, North-East Japan, West Japan and first-SIGNAL studies. Patients were selected either on the basis of known EGFR mutations or based on clinicopathologic criteria – non-smokers with adenocarcinomas – associated with increased likelihood of EGFR mutations.

**Results:** Nearly 2000 patients were enrolled on these four trials. Median ages ranged from 57 to 64 years. Seventy-six percent were women and 86% were non-smokers. Overall, gefitinib was associated with significantly less toxicity than chemotherapy and improved quality-of-life. Gefitinib also produced higher response rates in the EGFR mutation-positive patients (72% vs. 38%, odds ratio 4.04, p < 10\(^{-15}\)), as well as improved progression-free survival (PFS; hazard ratio 0.45, p < 10\(^{-16}\)). Overall survival (OS) was not significantly different between treatment groups (p = 0.35).

**Conclusions:** This meta-analysis confirms the results of each individual study and narrows the confidence intervals of these results. In patients with known EGFR mutations or whose tumors are likely to harbor a mutation, upfront gefitinib or chemotherapy are associated with similar OS. Gefitinib is associated with less fatigue, myelosuppression and nausea than chemotherapy (but produces more skin rash, diarrhea and pneumonitis). Patients receiving gefitinib have improved quality-of-life compared to those receiving chemotherapy, making it an appropriate first-line choice.

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1. Introduction

Gefitinib is an oral epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI). The EGFR is a member of the ERBB transmembrane growth factor receptor family [1]. Activation of the EGFR leads to downstream signaling cascades that are potent regulators of intracellular and intercellular processes, such as cell cycle progression, apoptosis and cell survival, proliferation, angiogenesis and metastasis [2].

EGFR is over-expressed in non-small cell lung cancer (NSCLC), where some studies demonstrated a correlation between higher EGFR expression and a more advanced cancer stage and poorer prognosis [3–5].

Gefitinib was initially approved by the US Food and Drug Administration (FDA) for the treatment of platinum- and docetaxel-refractory NSCLC based on a randomized phase II study of two different doses of gefitinib [6]. However, a subsequent phase III trial comparing gefitinib with placebo did not reveal a survival benefit in the overall intent-to-treat patient population [7]. Similarly, trials that added gefitinib to chemotherapy did not demonstrate any benefit for the combination [8,9]. Because of these disappointing results, the FDA withdrew its approval in 2005.

At around this time, there was increasing recognition from the completed phase II and III trials that patients with a particular clinicopathological phenotype appeared to derive more benefit from gefitinib (and also from erlotinib, another EGFR TKI). These patients
tended to be women, of Asian ethnicity, never-smokers and had tumors with adenocarcinoma histology [8,10–14]. Intensive translational analyses subsequently identified the presence of activating mutations within the EGFR in this subset of patients that explained their sensitivity and response to anti-EGFR TKI therapy [15–18].

On the basis of these observations, four randomized phase II I studies have compared first-line gefitinib vs. chemotherapy in East Asian patients with advanced NSCLC [19–22]. Three of these studies – the IPASS study and those by the North-East Japan and West Japan Study Groups – have been published, while results of the first-SIGNAL study have been reported in abstract form. Each of these studies demonstrated an improvement in objective response rates (ORRs) and progression-free survival (PFS) for the gefitinib arms, especially in patients whose tumors contained activating EGFR mutations.

Here, we perform a meta-analysis of the most updated results of these studies to better quantify the toxicities and clinical benefits of gefitinib over chemotherapy.

2. Methods

2.1. Study selection

We performed search of several engines, including Pubmed, Embase, Lilacs and the Johns Hopkins University Medical Library using the keywords “EGFR mutation” and “gefitinib” and limiting the results to randomized clinical trials. This yielded 43 citations, which were manually reviewed to identify three published studies. Abstracts presented at the annual conferences of major oncology meetings were also searched to identify the unpublished first-SIGNAL study. Together, these four studies evaluated gefitinib vs. chemotherapy for the first-line therapy of patients with advanced (stage IIIb/IV) NSCLC. These studies were similarly designed and enrolled similar patients, with the notable exception that two each enrolled patients with known EGFR mutations identified by polymerase chain reaction methods (the North-East Japan and West Japan Study Group studies) or patients with clinical characteristics (never- or light-smokers with adenocarcinomas) known to be associated with the presence of EGFR mutations (the IPASS and the first-SIGNAL studies).

On these trials, patients were randomized either to gefitinib 250 mg daily or platinum-based chemotherapy: carboplatin AUC 5–6/paclitaxel 200 mg/m² every 21 days (North-East Japan Study Group and IPASS studies), cisplatin 80 mg/m²/docetaxel 60 mg/m² every 21 days (West Japan Study Group) or cisplatin 80 mg/m² Day 1/gemcitabine 1250 mg/m² Days 1 and 8 every 21 days (first-SIGNAL). The primary end-point of these trials was either progression-free survival (North-East Japan, West Japan and IPASS studies) or overall survival (OS: first-SIGNAL study). Other end-points included ORRs and toxicities of the treatment arms. Responses were adjudicated according to RECIST criteria, while toxicities were assessed using the CTCAE, version 3.0.

2.2. Statistical analysis

Overall log-hazard ratios for PFS and OS were estimated using a weighted mean of log-hazard ratios from the individual studies with each weight proportional to the reciprocal of the corresponding variance estimate. Overall log-odds ratios for ORR and toxicities were estimated using the Mantel–Haenszel procedure.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Patient demographics.</th>
</tr>
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<tbody>
<tr>
<td>Characteristic</td>
<td>Gefitinib (n = 809)</td>
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<tr>
<td>Sex</td>
<td>194 (24%)</td>
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<tr>
<td>Male</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>615 (76%)</td>
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</table>

ECOG/WHO, Eastern Cooperative Oncology Group/World Health Organization.

3. Results

3.1. Patient characteristics

Nine hundred and sixty-nine and 960 patients, respectively, were randomized to receive either gefitinib or chemotherapy. The IPASS study was the largest of the four and randomized over 1200 patients. The other studies randomized between 172 and 309 patients.

Patient demographics are shown in Table 1. The median ages of patients ranged from 57 to 64 years-old. Based on the eligibility criteria of the trials, most patients were female (76%) and never-smokers (87%). More than 90% of patients had an Eastern Cooperative Oncology Group performance status of 0/1.

3.2. EGFR mutations

Both the North-East Japan and West Japan studies mandated the presence of an activating EGFR mutation prior to study entry. The IPASS and first-SIGNAL studies selected light- or never-smokers (<10 pack-years) with adenocarcinoma histology and subsequently analyzed available tumor tissue from consenting patients for EGFR mutations. The IPASS study recruited in East and South-east Asia (but not Korea) while the first-SIGNAL study exclusively enrolled Korean patients. In the IPASS study, analysis was performed on 36% of patients; of these patients, 57% were found to have activating EGFR mutations. In the first-SIGNAL study, 31% of patients had analyzable tumors; activating mutations were found in 44%.

From the four studies, data on specific activating EGFR mutations are available for 650 patients. Fifty-three percent were deletions in exon 19, 45% were the L858R mutation in exon 21 and 4% were other mutations (some tumor samples had multiple mutations). Of note, 11 of 437 samples (2.5%) analyzed in the IPASS study were found to contain the exon 20 T790M mutation, which is known to confer resistance to EGFR TKIs.

3.3. Toxicities

Toxicities reported on these trials are consistent with the known toxicities of gefitinib and the respective chemotherapy regimens. Representative toxicities include fatigue, which was significantly more common in the chemotherapy arms. In the North-East Japan, West Japan and IPASS studies, the cumulative incidence of fatigue of any grade in the gefitinib arms was 18% (148 of 808) vs. 46% (363 of 790) in the chemotherapy arms (odds ratio 0.24.
p < 10^{-15}). Nausea was also more common in the chemotherapy arms of the North-East Japan and IPASS trials, where 51% (344 of 677) of the patients experienced any grade nausea vs. 17% (116 of 694) in the gefitinib arms (odds ratio 0.19, p < 10^{-15}). Patients receiving chemotherapy also experienced significantly more myelosuppression. As an example, the incidence of all-grade and grade ≥ 3 neutropenia was much less common in the gefitinib arms (7% vs. 84% and 3% vs. 69%, respectively). Across the studies, the odds ratio for grade ≥ 3 neutropenia for gefitinib vs. chemotherapy was 0.01 (p < 10^{-15}).

On the other hand, rash and diarrhea were more common in the gefitinib arms. Sixty-nine percent (557 of 808) of patients in the gefitinib arms experienced any-grade rash vs. 21% (164 of 790) of patients in the chemotherapy arms (odds ratio 8.19, p < 10^{-15}). There was a similarly increased incidence of grade ≥ 3 rash for the gefitinib arms (3% vs. 1% odds ratio 3.39, p = 0.003). Any-grade diarrhea occurred in 46% (369 of 808) of the gefitinib-treated patients vs. 22% (170 of 790) of patients who received chemotherapy (odds ratio 3.15, p < 10^{-15}; grade ≥ 3 diarrhea was also more common (3% vs. 1%, odds ratio 3.12, p = 0.006). Pneumonitis, a rare but serious toxicity associated with gefitinib, was reported in the North-East Japan study in 5% (6 of 114) of gefitinib-treated patients vs. 0 of 113 patients in the chemotherapy arm (odds ratio ∞, p = 0.003). In the IPASS study, interstitial lung disease events (which included pneumonitis) occurred in 2.6% of gefitinib treated patients vs. 1.4% of those who received chemotherapy (odds ratio 1.97, p = 0.15).

### 3.4. Quality of life (QoL) analyses

QoL was analyzed in both the IPASS and first-SIGNAL studies. In the IPASS study, QoL was analyzed using the FACT-L, TOI and LCS instruments. The gefitinib group had better QoL and nominal symptom reduction compared to the chemotherapy group, with odds ratios (p values) for the respective measures of 1.34 (0.01), 1.78 (<0.001) and 1.13 (0.30). Patients with EGFR mutations treated with gefitinib had sustained clinical improvements over the chemotherapy group. Odds ratios (p values) for the various measures were 3.01 (p < 0.001), 3.96 (p < 0.0001) and 2.70 (p = 0.0003). Conversely, EGFR mutation-negative patients did worse when treated with gefitinib as compared to chemotherapy (0.31 (p = 0.002), 0.35 (p = 0.01) and 0.28 (p = 0.0002)).

The first-SIGNAL study also performed QoL analyses using the EORTC QLC-C30 and QLC-LC13 scales. They demonstrated improved global health status (p = 0.0007), role function (p = 0.007) and social function (p = 0.002) for the gefitinib patients compared to those who received chemotherapy.

### 3.5. Objective response rates

In the IPASS study, the ORR in the overall population was significantly higher in the gefitinib arm than in the chemotherapy arm (43% vs. 32%; odds ratio 1.59, p = 0.001). When stratified by EGFR mutational status, ORRs were higher in the mutation-positive patients for both treatments but especially for gefitinib. In the EGFR mutation-positive patients, the ORRs were 71% in the gefitinib arm vs. 47% in the chemotherapy arm (p < 0.001); in the EGFR mutation-negative patients, the ORRs were 1% vs. 24% respectively (p = 0.001).

There was a similar difference in ORR depending on EGFR mutation status in the first-SIGNAL study. In this study, the ORR in the overall population was also higher in the gefitinib arm (54% vs. 45%), although this was not statistically significant (p = 0.15). However, the disease-control rate (complete + partial responses + stable disease) was 67% in the gefitinib arm vs. 79% in the chemotherapy arm for the overall population (p = 0.017). When stratified by EGFR mutation status, the ORRs for the mutation-positive patients were 85% vs. 38% in the gefitinib vs. chemotherapy arms respectively (p = 0.002) and, in the mutation-negative patients, were 26% and 52% respectively (p = 0.051).

In the North-East Japan and West Japan studies, which only enrolled patients with EGFR mutations, the ORRs were 74% and 62% respectively in the gefitinib arms vs. 31% and 32% in the chemotherapy arms (p < 0.001 and p < 0.0001).

In the IPASS and first-SIGNAL studies, the ORR in the overall population for the gefitinib vs. chemotherapy groups was 45% vs. 35%. The overall estimated odds ratio is 1.53 (95% CI, 1.25 to 1.89, p = 6 × 10^{-5}). Across all four studies, the ORR in the EGFR mutation-positive patients was 72% in the gefitinib groups vs. 38% in the chemotherapy arms. The overall estimated odds ratio is 4.04 (95% CI, 2.90 to 5.61, p < 10^{-15}).

### 3.6. Progression-free survival

The primary end-point of the IPASS study was to demonstrate non-inferiority of gefitinib when compared to chemotherapy in terms of PFS. The primary end-point was met and, in fact, superiority of gefitinib over chemotherapy was demonstrated. In the overall population of the IPASS study, PFS was significantly longer in the gefitinib-treated patients. While median PFS was not different compared to the chemotherapy group (5.7 vs. 5.8 months), the 12-month PFS rate was 25% vs. 7% respectively (hazard ratio for progression 0.74, p < 0.001). Stratification by the EGFR mutation status confirmed that gefitinib produced a longer PFS in the mutation-positive patients (hazard ratio 0.48, p < 0.001) but was inferior to chemotherapy in the mutation-negative patients (hazard ratio 2.85, p < 0.001).

PFS benefit for gefitinib was strikingly similar in the first-SIGNAL study. The median PFS for the gefitinib vs. chemotherapy arms was 6.1 vs. 6.6 months respectively, while the 12-month PFS was 20% vs. 5% (p = 0.04). In the EGFR mutation-positive patients, however, there was only a non-significant trend toward improved PFS for the gefitinib over chemotherapy arms (median PFS 8.4 vs. 6.7 months, p = 0.084). Conversely, there was a non-significant trend toward improved PFS for the chemotherapy arm in the EGFR mutation-negative patients (median PFS 2.1 vs. 6.4 months, p = 0.071).

In the North-East Japan and West Japan studies, there was clear superiority of the gefitinib arms in terms of PFS. In the North-East Japan study, median PFS was 10.8 vs. 5.4 months (p < 0.001); the 12- and 24-month PFS were 42% and 8% in the gefitinib arm vs. 3% and 0% in the chemotherapy arm. In the West Japan study, median PFS was 9.2 vs. 6.3 months (p < 0.0001).

In the IPASS and first-SIGNAL studies, the estimated hazard ratio in the overall population is 0.76 (95% CI, 0.67–0.85, p = 3 × 10^{-6}). Across the four studies, the estimated hazard ratio in the EGFR mutation-positive patients is 0.45 (95% CI, 0.38–0.55, p = 10^{-16}). The individual and combined results for the EGFR mutation-positive groups are summarized in Fig. 1.

### 3.7. Overall survival

None of the studies has shown an OS benefit for gefitinib over chemotherapy, even in EGFR mutation-positive patients. Final OS data from the West Japan study are not yet mature but there is currently no significant difference between the gefitinib and chemotherapy patients (hazard ratio 1.64, p = 0.211). OS results for the IPASS study were recently updated in abstract form [23]. They show a similar median OS for the gefitinib vs. chemotherapy arms in the overall population (18.8 vs. 17.4 months, p = 0.109) as well as for patients who were EGFR mutation-positive (21.6 vs. 21.9 months, p = 0.99) and negative (11.2 vs. 12.7, p = 0.309). Forty-nine percent of the patients who initially received gefitinib were subsequently treated with carboplatin/paclitaxel.
chemotherapy at progression, while 51% of those who received initial chemotherapy were treated with an EGFR TKI after progressing.

In the first-SIGNAL study, median OS was similar in the gefitinib and chemotherapy arms in the overall population (21.3 vs. 23.3 months, $p = 0.428$) and the EGFR mutation-positive patients (30.6 vs. 26.5 months, $p = 0.648$). The proportion of patients who received additional therapy at progression was not discussed.

Finally, median OS in the North-East Japan study was also similar between the gefitinib and chemotherapy arms (30.5 vs. 23.6 months, $p = 0.31$). In this study, 112 patients who had progressed on upfront carboplatin/paclitaxel, 95% received second-line gefitinib, to which 56% had a response.

In the IPASS and first-SIGNAL studies, the estimated hazard ratio for death in the overall population between the gefitinib and chemotherapy groups is 0.94 (95% CI 0.80–1.09, $p = 0.40$). As shown in Fig. 2, the overall hazard ratio in the EGFR mutation-positive subsets of the IPASS, first-SIGNAL and West Japan studies (the North-East Japan study did not provide a hazard ratio or confidence interval for OS) is 0.91 (95% CI 0.64–1.29, $p = 0.60$). Similarly, each study provided a $p$ value for the log-rank comparison in OS between both treatment groups. When these $p$ values are combined using Fisher’s method for combining $p$ values, there is no significant difference in OS between treatment groups ($p = 0.35$).

3.8. Impact of specific EGFR mutations

As previously noted, the most common EGFR mutations are deletions in exon 19 and the L858R mutation of exon 21. In the IPASS study, the ORR for gefitinib vs. chemotherapy was 85% vs. 43% in the exon 19 deletions subgroup, compared to 61% vs. 53% in the L858R mutation subgroup. The hazard ratio for PFS for gefitinib vs. chemotherapy was 0.38 (95% CI 0.25–0.56) in the exon 19 deletion subgroup and was 0.55 (95% CI 0.35–0.87) in the L858R mutation subgroup [24]. A comparison of these subgroups revealed insufficient evidence to conclude that they respond differently to gefitinib vs. chemotherapy ($p = 0.23$). In the West Japan study, there was no difference in PFS between the exon 19 deletion and L858R mutation subgroups (median PFS 9.0 vs. 9.6 months, hazard ratio 1.13, 95% CI 0.63–2.03, $p = 0.68$).

Based on these limited data, it is not possible to determine if the specific EGFR mutation affects response to gefitinib.

4. Discussion

We performed this meta-analysis to better quantify the benefits and toxicities of gefitinib compared to chemotherapy in patients with activating EGFR mutations or with clinical characteristics that make these mutations more prevalent. The results of our meta-analysis confirm the results of the individual trials: initial gefitinib is associated with a higher ORR and PFS as well as superior toxicity and QoL profiles as compared to chemotherapy. These benefits are seen in Asian patients who are selected by clinicopathologic characteristics associated with the presence of an EGFR mutation but are even more pronounced in patients with known EGFR mutations. In these studies, there was no OS benefit for upfront gefitinib over chemotherapy, quite possibly because most patients treated initially with chemotherapy received and benefited from an EGFR TKI at progression.

Clearly, a major limitation of this meta-analysis is that it was performed on abstracted data rather than individual patient data. The limitations of such a meta-analysis are well-known and include an inability to verify and update patient data as well as a limited ability to calculate overall PFS and OS [25]. Nevertheless, the four trials that were analyzed are rigorously-performed randomized trials, three of which have been published in outstanding, high impact, peer-reviewed journals. The trials enrolled relatively similar patient populations, the survival data that are reported are mature and the results of each trial are in essential agreement with each other. As such, there should be few concerns about the accuracy of the data or any heterogeneity of the results of our meta-analysis.

Another caveat is that the results of the first-SIGNAL study have only been presented in abstract form. In addition, some of the data from this trial are puzzling. The ORR to gefitinib in patients who were found to be EGFR mutation-negative was 26%, which is unexpectedly high based on the currently accepted mechanism of action of this drug and when compared to the IPASS study (which reported an ORR of 1%). One possible explanation is that the methodology used in this study may have lacked sufficient sensitivity to detect all EGFR mutations so that patients who were labeled as EGFR mutation-negative may in fact have had undetected mutations. This explanation would also explain the lower EGFR mutation rate noted on this study (44%, compared to 57% in the IPASS study) even though both studies enrolled very similar patient populations. If this supposition were true, the conclusions of this study would still remain valid since patients who were incorrectly labeled as being EGFR mutation-negative would only decrease the magnitude of the observed benefit for gefitinib in EGFR mutation-positive vs. -negative patients.
An interesting conclusion of this meta-analysis is that there is a PFS benefit for gefitinib over chemotherapy even in patients selected because they are likely – but not absolutely known – to have tumors that harbor an EGFR mutation. While it remains preferable to determine the EGFR mutation status whenever possible, these data do justify the empiric use of gefitinib in patients who are likely to harbor such mutations but who are unable to undergo mutation analysis for some reason. Nevertheless, such a treatment strategy must be undertaken with the recognition that at least 40% of non-smokers with adenocarcinomas will be EGFR mutation-negative and would be unlikely to benefit from upfront treatment with gefitinib. Furthermore, the applicability of such an approach in a non-Asian population is unclear. Studies performed in North America have shown a noticeably lower frequency of EGFR mutations in those patients (ranging from 10–20% in larger trials, to 2% in a series of African American patients) [15–17]. In such patient populations, a strategy of empiric upfront gefitinib is not appropriate.

Finally, the lack of an OS benefit for initial gefitinib in these studies – in the overall population or even exclusively in patients with EGFR mutations – is a robust finding of this meta-analysis and apparent across almost all four studies. It suggests that patients with an acceptable performance status can be treated with either upfront chemotherapy or gefitinib. Even when patients progress on initial chemotherapy and presumably suffer some decrement in their fitness, they usually remain candidates for gefitinib because of its favorable toxicity profile. Hence, the initial treatment for such patients must be individualized based on their circumstances and preferences. It does remain likely that many patients and their physicians will choose upfront gefitinib because of its superior tolerability.

Conflict of interest

Dr. Lopes reports receiving research support and honoraria from AstraZeneca and Eli Lilly. There are no other potential conflicts of interest.

References