

Comparison of Gefitinib versus Docetaxel in Patients with Pre-Treated Non-Small Cell Lung Cancer (NSCLC)

More effective treatments in first, second, and third-line of metastatic non-small cell lung cancer (NSCLC) enable patients to live longer, with a better quality of life (QOL). Especially epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) contributed to this improvement. Gefitinib was compared with Docetaxel in four randomized trials, i.e., SIGN, Japanese V-1532, Korean ISTANA, and INTEREST in second or third-line treatment of metastatic NSCLC. In all the trials, and also by meta-analysis of 2,257 patients in these trials, Gefitinib was found non-inferior or superior to Docetaxel, with less toxicity, convenient oral administration, and better QOL. Detailed results are presented in the review article. Knowing that every line of treatment we may lose about 50% of patients for further treatment, it is very important to offer each patient the best option for every line of treatment. Gefitinib has a favorable benefit-risk profile compared with Docetaxel in this patient population. (*J Lung Cancer* 2009;8(2):61–66)

Key Words: Gefitinib, Docetaxel, 2nd line treatment, 3rd line treatment, Non-small cell lung carcinoma, Metastatic

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INTRODUCTION

Non-small cell lung cancer (NSCLC) represents 87% of all lung cancers and majority of patients present with metastatic stage disease at the time of diagnosis. The efficacy of platinum doublets, the most commonly used first-line regimen (1) for metastatic NSCLC, has reached a therapeutic plateau (2) and the introduction of a third chemotherapeutic agent increases toxicity without improving efficacy (3,4).

Only about 50% of patients in NSCLC clinical trials go on to receive second-line therapy and only about 50% of those will receive third-line therapy. It is therefore important to ensure that patients receive the best therapeutic option in each line of therapy (5).

In recent years, two new concepts have been introduced in the field of NSCLC: maintenance therapy and targeted biological agents. Two main groups of targeted agents in the treatment of NSCLC are epidermal growth factor receptor (EGFR) and vascular endothelial growth factor (VEGF) inhibitors. A wealth

of clinical data is available supporting the use of these agents in the treatment of metastatic NSCLC. EGFR inhibitors include cetuximab, gefitinib, and erlotinib.

This review will examine the treatment of trials comparing EGFR TKI Gefitinib vs. Docetaxel in second-line treatment of NSCLC addressing the questions of efficacy, quality of life (QOL), toxicity, and importance of a right sequencing of these agents.

Chemotherapy in Second Line Treatment

Patients with advanced NSCLC eventually relapse or are refractory to first-line treatment; acceptable toxicity and improved quality of life are especially important for these patients (while efficacy remains the main goal of therapy). Several chemotherapy agents, including Docetaxel and Pemetrexed, have demonstrated efficacy and have been approved by the FDA in the USA for second-line treatment of patients with locally advanced or metastatic NSCLC (6-8). As well, in Canada, approved second-line chemotherapy agents are intravenous docetaxel and intravenous pemetrexed - Pemetrexed for

non squamous histology only (9). Docetaxel has been reported to achieve response rates of 15~20% (6), overall survival (OS) of 8.3 months, and 1 year survival rates of up to 37%. However, docetaxel is associated with serious toxicities. Pemetrexed offers a similar median OS of 7.9 months, but with milder toxicity than docetaxel (8).

Targeted Therapies in Second Line Treatment - EGFR TKIs

Erlotinib plus Gefitinib are EGFR tyrosine kinase inhibitors (TKIs) that suppress intracellular signalling pathways, which normally promote cell growth and proliferation (10,11). Unlike chemotherapy, EGFR-TKIs have no cumulative haematological toxicities, allowing for a longer treatment duration. In contrast, the toxicities associated with chemotherapy only allow for a limited number of cycles (median approximately four cycles). Table 1 compares clinical data for erlotinib, docetaxel, and pemetrexed.

In a randomized, placebo-controlled study (BR.21), erlotinib demonstrated improvement in median OS (6.7 vs. 4.7 months) and quality of life across all subgroups (12-14).

Gefitinib failed to demonstrate a survival advantage vs. placebo in the overall population of a phase III trial (ISEL) (15), but 90% of patients were refractory to previous treatment and 10% intolerant to it. Asian population and never-smokers achieved a positive result - even in this population.

Table 1. Efficacy Data in the Second-Line Setting

Outcome	Erlotinib (150 mg daily)	Docetaxel (75 mg/m ² every 3 weeks)	Pemetrexed (500 mg/m ² every 3 weeks)
RR, %	8.9	6.7~8.8	9.1
Median duration of response, mo	7.9	5.3~9.1	4.6
Median PFS, mo	2.2	2.7~6	2.9
Median OS, mo	6.7	5.7~7.9	8.3
1-year survival, %	31	30~37	30
2-year survival, %	13	0	0
Median OS, mo in PS 0/1 patients with one prior regimen	9.4	9.1	9.4

RR: response rate, PFS: progression-free survival, OS: overall survival.

First trial which compared Docetaxel with Gefitinib was SIGN trial (16), Gefitinib 250 mg daily po was compared to Docetaxel 75 mg/m² i.v., every three weeks; 141 patients were randomized 1 : 1.

All patients were receiving second-line treatments, and 95% were non-Asian. Primary endpoint was symptom improvement, secondary endpoints included OS and progression-free survival (PFS). Median survival (MS) was 7.5 months vs. 7.1 months (hazard ratio [HR]=0.97) and median PFS was 3 months vs. 3.4 months (HR=0.94) for Gefitinib vs. Docetaxel, respectively. QOL and symptom improvement were better on Gefitinib arm, measured by FACT-L (i.e., Functional Assessment of Cancer Therapy - Lung) and LCS (Lung Cancer Subscale) (Fig. 1).

Next trial V-15-32 was Japanese phase III trial (17), 489 patients were randomized 1 : 1 to receive Gefitinib po 250 mg daily compared to Docetaxel 60 mg/m² i.v. every three weeks. Primary endpoint was OS. Median OS was 11.5 months vs. 14 months (HR=1.12) for Gefitinib vs. Docetaxel respectively and median PFS was 2 months for both treatments (HR=0.90). Post-study treatments were not well balanced as Docetaxel was given to only 36% of patients after Gefitinib, but 53% of patients after progression on Docetaxel received Gefitinib. Again QOL and symptom improvement were better on Gefitinib than on Docetaxel.

Korean study ISTANA (18) was comparing 82 patients on Gefitinib to 79 patients on Docetaxel. PFS at 6 months was

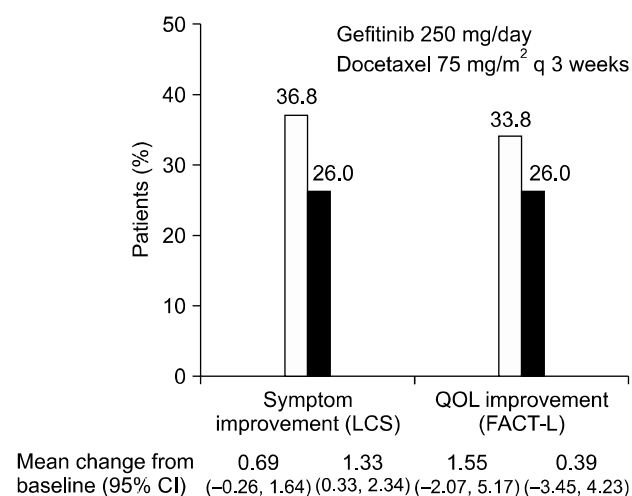


Fig. 1. SIGN: quality of life (QOL) & symptom improvement, LCS: lung cancer subscale, FACT-L: functional assessment of cancer therapy-lung, CI: confidence interval.

32% on Gefitinib and only 13% on Docetaxel, HR=0.729, p value 0.04 and OS was also better on Gefitinib with HR=0.606. Among Docetaxel-treated patients, 62% received subsequent EGFR-TKIs in contrast to only 26% of patients who started Gefitinib and went to Docetaxel. QOL and symptom improvement scales were again better on Gefitinib.

The largest study was INTEREST trial (19), phase III study of IRESSA (Gefitinib) vs. Docetaxel; patients must have received 1 or 2 chemotherapy regimens, at least one of them had to be platinum-based. 1,466 patients from 149 centers in 24 countries worldwide were randomized 1 : 1. Primary endpoints were OS, non-inferiority in all patients, but superiority in patients with high EGFR gene copy number (FISH positivity).

Mean time on treatment was 4.4 months for Gefitinib and 3 months for Docetaxel, median Docetaxel cycles administered were 4 (1-24). Never-smokers represented 20% of patients, Asian origin - 21% patients on Gefitinib (Table 2). Objective response rate was 9.1% vs. 7.6% on Gefitinib vs. Docetaxel, median PFS 2.2 months vs. 2.7 months (HR=1.04), median OS 7.6 months vs. 8 months, 1 year survival 32% vs. 34%, respectively (Table 3).

Patients with adenocarcinomas, females, never-smokers and Asian patients had better median OS on both Gefitinib and

Docetaxel, suggesting that these are also prognostic, not only predictive factors (Table 4). Patients who received two prior regimens did better on Docetaxel than on Gefitinib (MOS 11.9 vs. 6.9 months, p=0.03). About a third of the patients on each arm of treatment crossed over on this study, but no difference in survival was found, which means that Docetaxel after Gefitinib has the same efficacy as prior to Gefitinib. QOL and symptom improvement were better on Gefitinib (Fig. 2). The most frequent grade 3 and 4 toxicities on Gefitinib were rash and diarrhea, which were easy to manage. On Docetaxel, there was a higher incidence of neutropenia, febrile neutropenia, asthenia, and nausea grades 3 and 4. Alopecia was also associated with Docetaxel. FISH positive patients (47%) did not achieve superior survival on Gefitinib.

Higher mutation rates (20) were in never-smokers, Asian population, adenocarcinomas, and in females. They were associated with higher response rate (p=0.03) and longer PFS on Gefitinib, but not OS, which was longer in both arms, 14.2 months on Gefitinib and 16.6 months on Docetaxel compared to 6.4 and 6 months in mutation negative patients respectively.

Table 2. Demography (ITT Population) - INTEREST

	Gefitinib, % (n=733)	Docetaxel, % (n=733)
Age <65 years	61	67
Female	36	33
WHO PS 0/1/2*	30/58/12	25/63/12
Never-smoker*	20	20
Second-line*	84	83
Asian origin	21	23
Adenocarcinoma*	54	55
Since diagnosis: <6/6~12/>12 months	26/38/35	27/37/35
Prior platinum refractory [†] /received*	54/45	56/42
Prior paclitaxel refractory [†] /received/none*	9/9/81	8/9/82
Best response to previous CT (CR+PR)/SD/PD	27/41/26	31/38/25
Locally advanced disease	14	13

WHO: world health organization, CR: complete response, PR: partial response, SD: stable disease, PD: progressive disease.
*1 of the 6 stratification factors; [†]progressed during or within 3 months of completing therapy.

Table 3. Phase III Gefitinib vs. Taxotere: Overall Survival (INTEREST)

	Gefitinib	Taxotere	HR (CI)
Median survival time, overall population, mo	7.6 (n=659)	8.0 (n=657)	1.02 (95% CI: 0.905~1.150)
Median survival time, high EGFR population, mo	8.4 (n=85)	7.5 (n=89)	1.09 (95% CI: 0.78~1.51)

Non-inferiority demonstrated in overall population (95% CI upper limit <1.154). Superiority NOT demonstrated in high EGFR population (p=0.6199). HR: hazard ratio, CI: confidence interval, EGFR: epidermal growth factor receptor.

Table 4. INTEREST: Median Survival According to Clinical Factors

	Gefitinib	Docetaxel
Adenocarcinomas	8.5	8.9
Other histologies	6.4	6.9
Female	11.2	10
Male	6.1	7
Never-smokers	14.1	13.9
Smokers	6.4	6.9
Asian	10.4	12.2
Non-Asian	6.9	6.9

Patients with K-Ras mutations did not have shorter survival on Gefitinib (Table 5).

In conclusion, the INTEREST trial met the primary objective of demonstrating non-inferiority of Gefitinib relative to Docetaxel in terms of overall survival. There was no evidence from the co-primary analysis to support the hypothesis that patients with high EGFR gene copy number have superior overall survival on Gefitinib compared with Docetaxel. PFS and RR were similar on both treatments. Gefitinib was better tolerated and significantly more Gefitinib-treated patients experienced a

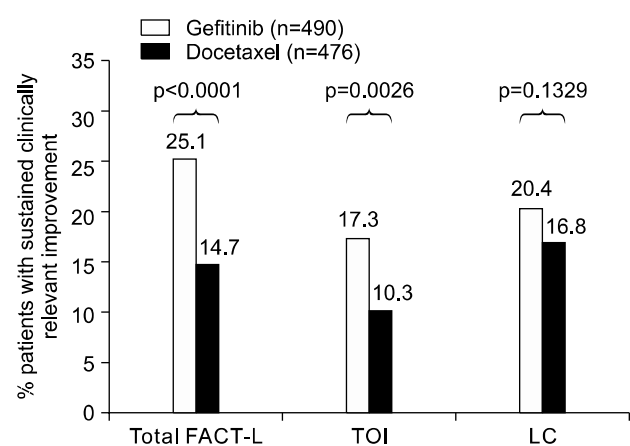


Fig. 2. Quality of life and symptom improvement rates (EFQ population) - INTEREST. p values from logistic regression with covariates. Clinically relevant improvement pre-defined as 6-point improvement for FACT-L and TOI; 2-point improvement for LCS, maintained for at least 21 days. EFQ: evaluable for quality of life, FACT-L: functional assessment of cancer therapy-lung, TOI: trial outcome index, LCS: lung cancer subscale.

clinically relevant improvement in QOL compared with Docetaxel. Overall survival was similar for Gefitinib and Docetaxel irrespective of EGFR gene copy number, EGFR protein expression, EGFR mutation, or K-Ras mutation status, but these findings should be interpreted in the context of exploratory analysis often based on small numbers of patients.

Given the lack of difference in clinical benefit relating to the sequence of chemotherapy versus EGFR-TKI for second-third line (INTEREST trial), as well as less toxicity and easy oral administration, EGFR-TKI agents are preferred second-line agents for NSCLC. Obtaining mutation status (EGFR exon 19 +21) of the tumour for second-line NSCLC treatment is not a necessity. K-ras mutations, when available in future, could also facilitate our decision for choice of treatment.

Meta-analysis (21) from the above-mentioned four clinical trials, 2,257 patients, demonstrated similar OS, PFS and superior RR for Gefitinib (Fig. 3) and the results were those of the individual study results. Given the similar or superior efficacy demonstrated by Gefitinib, its favourable tolerability profile and oral administration, Gefitinib has a favourable benefit-risk

Table 5. INTEREST: Overall Survival According to Biomarkers

	Gefitinib	Docetaxel
EGF- R+	7.9	6.5
EGF- R-	7.5	9.2
EGF- R mutant	14.2	16.6
EGF- R wild	6.4	6
K ras mutant	7.8	4.2
K ras wild	7.5	6.3

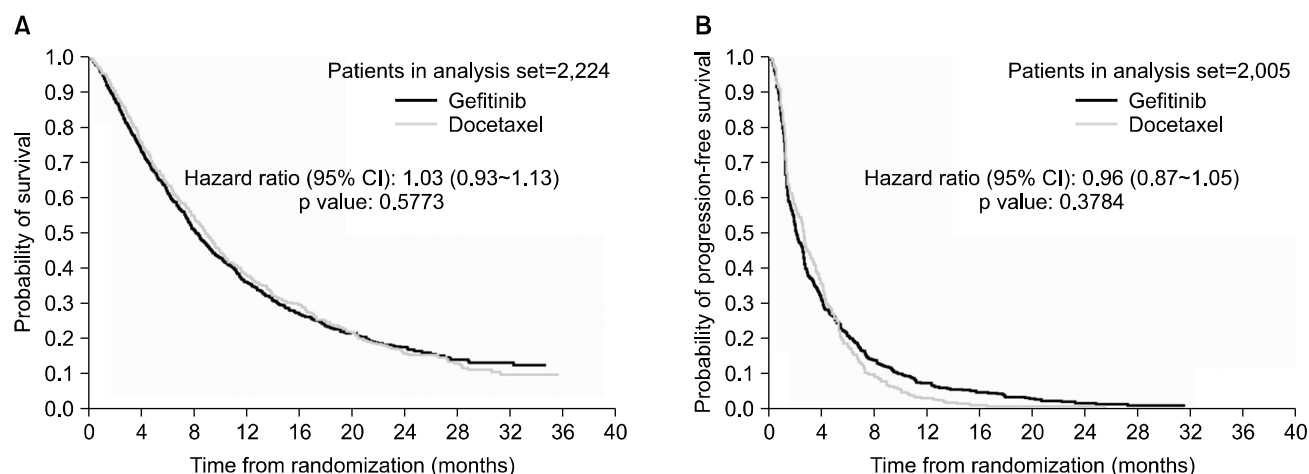


Fig. 3. Kaplan-Meier curves of (A) overall survival and (B) progression-free survival for all patients (Meta-analysis).

profile compared with Docetaxel in a pre-treated advanced NSCLC patient population.

Chemotherapy in Third Line Treatment

A retrospective practice review found that second-line erlotinib treatment is efficacious and well-tolerated, and does not diminish the benefit of third-line chemotherapy (22).

The use of erlotinib as third-line therapy is supported by the BR-21 study in which approximately half of patients had failed two previous lines of chemotherapy. In addition to its acceptable safety profile, erlotinib demonstrated clinical benefit in terms of response and OS in patients with a good or poor ECOG performance status. The non-inferiority of the EGFR TKI gefitinib over docetaxel in terms of OS (INTEREST trial) together with its improved safety profile and preferred oral administration over a longer period of time make EGFR TKIs prime candidates for second-line, rather than third-line treatment in patients with NSCLC. Educating physicians of the importance of rebiopsing the tumour at the time of progression to help guide our treatment decision in the future as well as optimal techniques of biopsies will be of utmost importance.

A number of trials are investigating the role of anticancer therapies in the third- or fourth line setting. BIBW 2992, a dual inhibitor of EGFR (Erb 1) and HER2, was evaluated in a phase IIb/III trial with BSC vs. placebo and BSC in NSCLC patients who had failed 1~2 lines of chemotherapy and erlotinib or gefitinib (LUX-LUNG 1). Interim results have been reported and the data monitoring committee has determined that the trial should continue to full accrual, which happened at the end of August 2009 (23). Two ongoing trials (phase II SUN-1058 and phase III SUN-1087) are exploring the combination of sunitinib with erlotinib as second- and third-line therapy. Results from the phase III trial ZEPHYR will help define the role of vandetanib in the third- and fourth-line setting after EGFR-TKI failure. Results from this trial are expected in early 2010. A phase III trial of sorafenib vs. placebo as third- and fourth-line therapy is currently recruiting patients - data are expected in April 2011. Combining an insulin-like growth factor (IGFR) inhibitor with erlotinib after progression of disease in second line to try to reverse resistance to erlotinib is also under investigation. Sufficient tumour biopsies will be essential to guide our decisions for treatment with targeted agents.

DISCUSSION

The main goal is to provide the best possible treatment in terms of both efficacy and safety in each line of therapy. The striking improvements in outcomes demonstrated in both first- and second-line settings with targeted therapies provide a rationale for their use. Targeting multiple pathways using a wide range of new drugs and combinations of agents is currently undergoing investigation.

Targeted agents may offer reduced toxicity compared with chemotherapeutic agents, especially with prolonged use. Combinations of targeted agents may also have potential as novel treatment paradigms, perhaps even representing an alternative to chemotherapy.

Predictors of response may help to guide individual treatment decisions; however, for most drugs clinically validated markers have not yet been identified. Until reliable biomarkers for response and resistance (old or newly developed during the therapy) are identified, differences in toxicity between chemotherapeutic and targeted agents may provide the best guide for individual treatment decisions in view of similar efficacy.

Gefitinib recently received EMEA approval in Europe for treatment of patients with EGFR mutation-positive disease. EGFR mutations can be viewed as predictive markers of high clinical benefit with EGFR TKI therapy, especially for first-line treatment in eligible patients.

An individualized, personalized targeted approach will be the treatment in future for all lines of treatment, but will require tumour rebiopsy for analysis of biomarkers, including not only newly developed markers of resistance to EGFR TKI, but also sensitivity to agents such as BIBW 2992 (T790M mutation and c-met amplification).

Defining predictors of tumour response and benefit from treatment by analysing circulating tumour cells and blood biomarkers is of a great need in the future.

CONCLUSION

Given the plateau reached with chemotherapy, and toxicity associated with prolonged chemotherapy, there is a need to improve outcomes in every line of therapy of advanced

NSCLC. Targeted biological agents are effective and well tolerated in NSCLC.

Novel targeted therapies and their combinations even with chemotherapeutic agents are also being explored. Future challenges revolve around identifying predictors of response and efficacy of targeted NSCLC therapies, as well as selecting the optimum therapy for maximum survival benefit in each line of treatment.

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