The emerging role of epidermal growth factor receptor (EGFR) inhibitors in first-line treatment for patients with advanced non-small cell lung cancer positive for EGFR mutations

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***Abstract*:** Gefitinib and erlotinib, small-molecule tyrosine kinase inhibitors (TKIs) of the epidermal growth factor receptor (EGFR), were the first molecularly targeted agents to become clinically available for the treatment of non-small cell lung cancer (NSCLC). During the course of their clinical development, it has become clear that the substantial clinical benefit associated with EGFR-TKIs is limited to patients harboring activating mutations of EGFR. Accumulating clinical outcomes in patients with EGFR mutation-positive NSCLC treated with EGFR-TKIs support the notion that this group of individuals constitutes a clinically distinct population. These findings have prompted investigations of the potential role of first-line treatment with EGFR-TKIs in molecularly selected patients, with platinum-based doublet chemotherapy currently being the standard of care for most individuals with advanced NSCLC. This review summarizes the results of recent clinical trials of EGFR-TKIs in selected patients and highlights the efficacy of these drugs in first-line treatment as a form of personalized medicine aimed at improving therapy for advanced NSCLC.

***Keywords*:** epidermal growth factor receptor mutation, first-line treatment, non-small cell lung cancer, tyrosine kinase inhibitor

Introduction

Non-small cell lung cancer (NSCLC) is the leading cause of death related to cancer worldwide [Jemal *et al*. 2009]. Cytotoxic chemotherapy remains the mainstay of treatment for individuals with metastatic NSCLC on the basis of the associated moderate improvement in survival and quality of life. The poor outlook even for patients with advanced NSCLC who receive such chemotherapy has prompted a search for new therapeutic approaches.

The development of targeted therapies is being actively pursued in order to improve treatment efficacy in select populations of cancer patients. The discovery that signaling by the epidermal growth factor receptor (EGFR) plays a key role in tumorigenesis prompted efforts to target this receptor in anticancer therapy [Mendelsohn and Baselga, 2003]. EGFR is frequently overexpressed in NSCLC and has been implicated in the pathogenesis of this disease. Small-molecule tyrosine kinase inhibitors (TKIs) that target EGFR, such as gefitinib and erlotinib, compete with adenosine triphosphate (ATP) for binding to the tyrosine kinase pocket of the receptor, thereby inhibiting receptor tyrosine kinase activity and EGFR signaling pathways [Okamoto, 2010]. Given the biological importance of EGFR signaling in NSCLC, EGFR-TKIs have been evaluated most extensively in individuals with this condition. Indeed, they have had a substantial impact on the treatment of this disease by offering additional therapeutic options for patients with advanced NSCLC.

Discovery of EGFR mutations and their association with response to EGFR-TKIs

Early clinical studies showed that a subset of patients with advanced NSCLC experienced

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a rapid, pronounced, and durable response to single-agent therapy with EGFR-TKIs [Nakagawa *et al*. 2003]. Subsequent retrospective analysis of clinical data consistently demonstrated that a clinical response to these agents is more common in women than in men, in Japanese than in individuals from Europe or the United States, in patients with adenocarcinoma than in those with other histological subtypes of cancer, and in individuals who have never smoked than in those with a history of smoking [Ando *et al*. 2006]. These clinical observations paved the way for translational research that aimed to identify at the molecular level patients who might benefit from such therapy. In 2004, three groups in the United States made the landmark observation that NSCLC patients who experienced a marked response to gefitinib or erlotinib commonly harbored somatic mutations in the gene for EGFR, the molecular target of these drugs [Lynch *et al*. 2004; Paez *et al*. 2004; Pao *et al*. 2004]. Indeed, EGFR mutations are present more frequently in women, in individuals of East Asian ethnicity, in patients with adenocarcinoma, and in those who have never smoked, the same groups identified clinically as most likely to respond to treatment with EGFR-TKIs.

EGFR mutation as a mechanism underlying sensitivity to EGFR-TKI therapy

The discovery of EGFR mutations led not only to the identification of a molecular predictor of sensitivity to EGFR-TKIs but also to examination of the effects of such mutations on EGFR function. Base-pair deletions in exon 19 and a point mutation (L858R) in exon 21 are the most common EGFR mutations as well as the most extensively evaluated to date. Initial studies based on transient transfection of various cell types with vectors encoding wild-type or mutant versions of EGFR showed that the extent of activation of mutant receptors by epidermal growth factor is more pronounced and sustained than is that of the wild-type receptor [Lynch *et al*. 2004]. Subsequently, NSCLC cell lines with exon-19 deletions or the L858R point mutation of EGFR were identified, and these mutations were found to confer the property of ligand-independent activation on EGFR [Okabe *et al*. 2007]. We also found that the constitutive activation of endogenous mutant EGFR is attributable to the ability of the mutant receptor to undergo ligand-independent dimerization [Okabe *et al*. 2007]. Introduction of either of the two most common EGFR mutants into transgenic mice was recently shown to result in the formation of lung adenocarcinomas, demonstrating that expression of these constitutively activated forms of EGFR is sufficient for transformation and required for maintenance of these tumors [Politi *et al*. 2006]. These various observations indicate that EGFR mutation-positive tumors are dependent on, or 'addicted' to, EGFR signaling for their growth and survival. Similar addiction is evident in chronic myelogenous leukemia positive for the BCR-ABL fusion gene and in KIT mutation-positive gastrointestinal stromal tumors, both of which are highly sensitive to imatinib. Exposure of EGFR mutation-positive NSCLC tumors to EGFR-TKIs thus results in EGFR signaling pathways being turned off and the cancer cells undergoing apoptosis. Moreover, EGFR mutations result in repositioning of critical residues surrounding the ATP binding cleft of the tyrosine kinase domain of the receptor and consequent stabilization of the interaction with EGFR-TKIs, leading to an approximately 100-fold increase in sensitivity to inhibition by these drugs compared with that of the wild-type receptor [Lynch *et al*. 2004; Sordella *et al*. 2004]. These factors combine to render EGFR mutation-positive NSCLC more sensitive to EGFR-TKIs.

Prospective single-arm trials of EGFR-TKIs for patients with EGFR mutation-positive advanced NSCLC

Several prospective clinical trials of gefitinib or erlotinib for treatment of NSCLC patients with EGFR mutations have been performed to date, revealing radiographic response rates of 55–91% [Rosell *et al*. 2009; Sugio *et al*. 2009; Sequist *et al*. 2008; Tamura *et al*. 2008; Sunaga *et al*. 2007; Yoshida *et al*. 2007; Inoue *et al*. 2006; Sutani *et al*. 2006] (Table 1). These values are much higher than those historically observed with standard cytotoxic chemotherapy for advanced NSCLC. As the data accumulate, an improvement in overall survival (OS) conferred by treatment with these drugs is also expected in patients harboring EGFR mutations. It was not possible to evaluate OS in most of the clinical trials at the time of publication because the number of patients was not sufficiently large and the follow-up period was not long enough to obtain precise estimates of survival outcome. Our group has recently analyzed updated individual patient

Table 1. Prospective study of epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitor monotherapy for non-small cell lung cancer patients with EGFR mutations.

Study	Agent	Patients	*n*	RR (%)
Asahina *et al.* [2006]	Gefitinib	First-line	16	75
Inoue *et al.* [2006]	Gefitinib	First-line	16	75
Sutani *et al.* [2006]	Gefitinib	Mixed	27	78
Sunaga *et al.* [2007]	Gefitinib	Mixed	19	76
Yoshida *et al.* [2007]	Gefitinib	Mixed	21	91
Sequist *et al.* [2008]	Gefitinib	First-line	34	55
Tamura *et al.* [2008]	Gefitinib	Mixed	28	75
Rosell *et al.* [2009]	Erlotinib	Mixed	217	71
Sugio *et al.* [2009]	Gefitinib	Mixed	19	63

Mixed, first line and subsequent lines; RR, overall response rate.

data from seven Japanese prospective phase II trials of gefitinib monotherapy, including a total of 148 EGFR mutation-positive individuals [Morita *et al.* 2009]. Our Iressa (gefitinib) Combined Analysis of Mutation Positives (I-CAMP) study showed that the overall response rate to gefitinib was 76.4% (95% confidence interval [CI], 69.5–83.2). With a median follow-up time of 20.7 months, gefitinib conferred a highly favorable progression-free survival (PFS) of 9.7 months and OS of 24.3 months in such patients. The Spanish Lung Cancer Group reported the results of a large prospective study for 217 EGFR mutation-positive individuals treated with erlotinib [Rosell *et al.* 2009]. The overall response rate was 70.6%, similar to that reported for gefitinib. With a median follow-up time of 14 months, the median PFS and OS for the 217 patients were 14 and 27 months, respectively. The median survival time of more than 2 years achieved in patients with EGFR mutation-positive NSCLC by EGFR-TKI treatment supports the notion that this group of individuals constitutes a clinically distinct population. These data also suggest that there is no major ethnic difference in the distinguished clinical effects of EGFR-TKI treatment for EGFR mutation-positive individuals.

EGFR-TKIs as first-line therapy for EGFR mutation-positive patients with advanced NSCLC

The substantial clinical benefit of EGFR-TKI treatment in EGFR mutation-positive NSCLC patients raises the question as to whether first-line EGFR-TKI treatment might be more beneficial than standard cytotoxic chemotherapy in this genotype-defined population. Jackman and colleagues established an Internet-based registry of clinical trials that use EGFR-TKIs for chemotherapy-naïve NSCLC patients whose tumors have been tested for EGFR mutations, and they reported pooled data from 84 patients with a sensitizing EGFR mutation who received either erlotinib or gefitinib as first-line treatment (Table 2) [Jackman *et al.* 2009]. The overall response rate, median PFS, and median OS were 67%, 11.8 months, and 23.9 months, respectively, indicating the potential value of first-line treatment with EGFR-TKIs in White patients with sensitizing EGFR mutations. In the I-CAMP study, we performed an exploratory comparison between gefitinib and systemic chemotherapy in the first-line setting (Table 2) [Morita *et al.* 2009]. Among the total of 148 EGFR mutation-positive NSCLC patients, 87 individuals received gefitinib as first-line therapy, whereas 61 received systemic chemotherapy as first-line treatment followed by gefitinib. The *post hoc* analysis revealed that the response rate was significantly higher for the first-line gefitinib group than for the first-line chemotherapy group (79.3% versus 24.6%, $p < 0.001$). Furthermore, the log-rank test demonstrated that PFS was significantly longer in the first-line gefitinib group than in the first-line chemotherapy group (median of 10.7 versus 6.0 months, $p < 0.001$), whereas there was no significant difference in OS between the two groups of patients (median of 27.2 versus 25.7 months, $p = 0.782$), likely because all patients treated with systemic chemotherapy as a first-line treatment received gefitinib as a subsequent treatment (Table 3). These data support the use of EGFR-TKIs as an initial therapy in this patient population and warrant the performance of prospectively designed randomized trials comparing EGFR-TKIs with platinum-based chemotherapy.

Table 2. Clinical studies assessing first-line treatment with epidermal growth factor (EGFR)-tyrosine kinase inhibitors for patients with EGFR mutation-positive non-small cell lung cancer.

Study	Agent	*N*	RR (%)	PFS (months)	OS (months)
Morita *et al.* [2009]	Gefitinib	87	79.3	10.7	27.2
Jackman *et al.* [2009]	Gefitinib	28	60	11.4	20.8
Jackman *et al.* [2009]	Erlotinib	56	70	13.0	28.7
Rosell *et al.* [2009]	Erlotinib	113	73.5	–	28.0

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

Table 3. Clinical studies assessing first-line treatment with epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitors compared with chemotherapy for patient with EGFR mutation-positive non-small cell lung cancer.

Study	*N*	Median PFS (months)			Median OS (months)	
		Gefitinib	Chemotherapy	HR (95% CI)	Gefitinib	Chemotherapy
Nonrandomized pooled analysis:						
I-CAMP	148	10.7	6.0	0.35 (0.23–0.52)	27.7	25.7
Sunset analysis of randomized phase III trial for clinically selected patients:						
IPASS	261	9.5	6.3	0.48 (0.36–0.64)	~20	~20
Phase III trials for EGFR mutation-positive NSCLC patients:						
WJTOG3405	172	9.2	6.3	0.49 (0.37–0.71)	–	–
NEJ002	194	10.4	5.5	0.36 (0.25–0.51)	28.0	23.6

CI, confidence interval; HR, hazard ratio; I-CAMP, Iressa Combined Analysis of Mutation Positives study; IPASS, IRESSA Pan Asia Study; NEJ002, North East Japan Gefitinib Study Group 002 trial; OS, overall survival; PFS, progression-free survival; WTJTOG3405, West Japan Thoracic Oncology Group 3405 trial.

IPASS (IRESSA Pan Asia Study) and the First-Signal study were randomized phase III trials that compared gefitinib with a standard platinum doublet chemotherapy as first-line treatment for patients with lung adenocarcinoma who were never-smokers or former light smokers [Lee *et al.* 2009; Mok *et al.* 2009]. In the IPASS trial, the 1217 patients were randomized to receive either 250 mg of gefitinib daily ($n = 609$) or both carboplatin (area under the curve of 5 or 6) and paclitaxel (200 mg/m^2) ($n = 608$). The study exceeded its primary endpoint of showing the noninferiority of gefitinib by demonstrating its superiority compared with carboplatin paclitaxel in terms of PFS. However, the IPASS and the First-Signal study demonstrated that the PFS curves crossed at around 6 months after the start of treatment, favoring chemotherapy during the initial 6 months and gefitinib thereafter, suggesting the existence of two different patient populations in terms of response to gefitinib and chemotherapy even among the clinically selected patients. Exploratory biomarker analysis for about a third of the patients enrolled onto the IPASS study revealed that about 60% of individuals harbored EGFR mutations in their tumor cells. For the EGFR mutation-positive group, first-line gefitinib treatment showed a significantly better response rate (71.2 versus 47.3%, $p < 0.001$) and longer PFS (hazard ratio [HR], 0.48; 95% CI, 0.36–0.64; $p < 0.001$) compared with treatment with carboplatin and paclitaxel, whereas there was no significant difference in OS between the two treatment groups (HR, 0.78; 95% CI, 0.50–1.20), possibly as a result of crossover to the comparator treatment (Table 3). Significantly more EGFR mutation-positive patients treated with gefitinib experienced a clinically relevant improvement in quality of life compared with those treated with carboplatin paclitaxel, as assessed by scores on the Functional Assessment of Cancer Therapy–Lung (FACT-L: 70.2% versus 44.5%, $p < 0.0001$), the Trial Outcome Index (TOI: 70.2% versus 38.3%, $p < 0.0001$), and Lung Cancer Subscale (LCS: 75.6% versus 53.9%, $p = 0.0003$). The IPASS trial was originally designed to assess first-line gefitinib treatment in clinically enriched patients according to such characteristics as the presence of adenocarcinoma histology and smoking history; however, the additional subgroup analysis for only a third of the enrolled subjects strongly supported the

clinical benefit of first-line therapy with gefitinib in EGFR mutation-positive NSCLC patients.

We have recently completed a multicenter, randomized, open-label, phase III trial (West Japan Thoracic Oncology Group [WJTOG] 3405) of first-line treatment with gefitinib versus cisplatin plus docetaxel for advanced NSCLC with activating mutations of EGFR [Mitsudomi *et al.* 2010]. Patients were eligible if they had histologically or cytologically confirmed NSCLC (stage IIIB or IV, or postoperative recurrence) harboring activating EGFR mutations (either an exon-19 deletion or L858R in exon 21), were aged 75 years or younger, had a World Health Organization (WHO) performance status (PS) of 0 or 1, had measurable or nonmeasurable disease according to the Response Evaluation Criteria in Solid Tumors (RECIST), and had adequate organ function. The primary endpoint was PFS in order to demonstrate the superiority of gefitinib over cisplatin docetaxel in these patients. While this trial was ongoing, however, the IPASS results were presented at the annual meeting of the European Society for Medical Oncology (12–16 September 2008 in Stockholm, Sweden), revealing the HR for improvement in PFS in the EGFR mutation-positive patients receiving gefitinib to be 0.48 ($p < 0.001$) (Table 3). Furthermore, the North East Japan Gefitinib Study Group presented the results of their phase III trial (002) at the annual meeting of the American Society of Clinical Oncology (29 May to 2 June 2009 in Orlando, FL) [Kobayashi *et al.* 2009]. In this study, 198 NSCLC patients with EGFR mutations were randomized to receive treatment with either gefitinib or carboplatin paclitaxel, and the HR for PFS with gefitinib compared with that with carboplatin paclitaxel was 0.36 (Table 3). Under these circumstances, the independent data and safety monitoring committee of the WJTOG3405 approved a protocol amendment regarding the sample size and final analyses to be performed. Between 31 March 2006 and 22 June 2009, a total of 172 patients were randomly assigned to receive either 250 mg of gefitinib daily ($n = 86$) or both docetaxel (60 mg/m^2) and cisplatin (80 mg/m^2) ($n = 86$). At the cutoff time for data collection, the median follow-up time was 81 days (range, 74–1253), the median exposure time to gefitinib was 165 days (range, 22–1100), and the median number of cycles of cisplatin docetaxel chemotherapy was four (range, one to six). Median PFS was 9.2 months (95% CI, 8.0–13.9) in the gefitinib group and 6.3 months (95% CI, 5.8–7.8) in the cisplatin docetaxel group ($p < 0.0001$). The study thus met its primary endpoint and demonstrated the superiority of gefitinib over cisplatin docetaxel in terms of PFS in the first-line setting (HR, 0.489; 95% CI, 0.37–0.71; $p < 0.0001$) (Table 3). In this trial, 71 patients (41%) had postoperative recurrent disease, and the remaining 101 individuals (59%) had stage IIIB or IV disease. Although PFS in the gefitinib group was longer than that in the cisplatin docetaxel group for both of these patient subsets, the benefit of gefitinib was more prominent in patients with stage IIIB or IV disease. Patients with stage IIIB or IV disease assigned to gefitinib ($n = 51$) had a median PFS of 8.4 months, whereas those assigned to cisplatin docetaxel had a median PFS of 5.3 months (HR, 0.33; 95% CI, 0.20–0.54; $p < 0.0001$). This result is thus similar to that of the NEJ002 trial, which reported a HR of 0.36 (95% CI, 0.25–0.51) for gefitinib compared with carboplatin paclitaxel in patients with EGFR mutations (Table 3). The PFS benefit for gefitinib did not seem to translate into an obvious survival benefit in the WJTOG3405 trial, although data for OS were premature with only 17 deaths in the gefitinib group versus 10 deaths in the cisplatin docetaxel group (HR, 1.638; 95% CI, 0.75–3.58). Although the WJTOG3405 trial did not provide quality-of-life data, several randomized phase III studies have shown that the tolerability profile of gefitinib is better than that of systemic chemotherapy, resulting in an improvement in quality of life. Given the favorable efficacy and toxicity profile of gefitinib compared with conventional chemotherapy, it is appropriate to consider patients with known sensitizing mutations of EGFR for first-line therapy with EGFR-TKIs.

These various clinical trials evaluating the role of EGFR-TKIs in the treatment-naïve setting have been performed in patients with a good PS. Yang and colleagues retrospectively analyzed 76 poor-PS (PS 3 or 4) chemotherapy-naïve NSCLC patients who received gefitinib as first-line treatment and demonstrated that women, adenocarcinoma or nonsmoking status, the same groups identified as most likely to have EGFR mutations, were good predictive factors of long survival time [Yang *et al.* 2006]. Inoue and colleagues performed a phase II study to evaluate the efficacy and feasibility of first-line gefitinib treatment for EGFR mutation-positive NSCLC

patients with a poor PS [Inoue *et al.* 2009]. Twenty-nine patients, including 22 individuals with a PS of 3 or 4, were subjected to first-line treatment with gefitinib, resulting in an overall response rate of 66%, a value similar to those obtained for EGFR-TKI treatment in EGFR mutation-positive patients with a good PS. The median PFS and OS were 6.5 and 17.8 months, respectively: values that are three to four times those generally observed with conventional cytotoxic chemotherapy in such a patient population. Moreover, an improvement from PS 3 to 4 at baseline to PS 0 to 1 was observed in 68% of patients. These data thus suggest that the efficacy of EGFR-TKIs in patients with EGFR mutations overcomes the compromised function of individuals with a poor PS who might not be eligible to receive systemic chemotherapy. First-line therapy with EGFR-TKIs should thus be more readily considered for EGFR mutation-positive patients with a poor PS, in whom the efficacy of systemic chemotherapy is clearly limited.

Conclusion

The discovery of somatic mutations in the tyrosine kinase domain of EGFR and of the association of such mutations with a high response rate to EGFR-TKIs has had a profound impact on the treatment of advanced NSCLC. Two recently completed randomized phase III trials (WJTOG3405, NEJ002) comparing platinum-based chemotherapy with gefitinib in chemotherapy-naïve NSCLC patients with sensitizing EGFR mutations, have provided strong evidence that first-line treatment with EGFR-TKIs should be considered an important standard therapeutic option for such patients.

Conflict of interest statement

The authors declare they have no conflicts of interest.

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