Review

Progress in individualized treatment for *EGFR*-mutated advanced non-small cell lung cancer

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Abstract: The identification of mutations in the epidermal growth factor receptor (*EGFR*) gene has revolutionized the treatment strategy for non-small cell lung cancer (NSCLC). The effectiveness of individualized treatment using EGFR tyrosine kinase inhibitors (TKIs) for *EGFR*-mutated NSCLC has mainly been clarified in clinical trials within Japan, and EGFR-TKI monotherapy has been established as the standard first-line treatment for *EGFR*-mutated NSCLC. Since then, combination regimens involving EGFR-TKI and chemotherapy or anti-angiogenic agents have been developed. Regarding combinations, the NEJ009 study conducted in Japan showed a significant prolongation of progression-free survival and overall survival compared with gefitinib alone. The NEJ009 regimen may be a reasonable option for patients with good performance status in terms of risk–benefit balance. However, further investigation is warranted to improve clinical outcomes in *EGFR*-mutated NSCLC.

Keywords: lung cancer, EGFR-TKI, *EGFR* mutation, chemotherapy

Introduction

Lung cancer is a leading cause of cancer death worldwide, and the median survival time (MST) of patients with advanced lung cancer was reported to be around 1 year in the early 2000s, even if they were treated with standard therapies such as platinum-based chemotherapy followed by docetaxel.[1] Gefitinib, the first epidermal growth factor receptor (*EGFR*) tyrosine kinase inhibitor (TKI), was approved in 2002 in Japan for advanced non-small cell lung cancer (NSCLC), which accounts for about 80% of all lung cancers. However, the response rate and progression-free survival (PFS) with gefitinib as a second-line treatment for unselected NSCLC patients was 18% and 2.7 months, respectively, which did not differ from docetaxel.[2] Additionally, the IRESSA Survival Evaluation in Lung Cancer trial conducted in western countries demonstrated that gefitinib did not improve overall survival (OS) of patients with NSCLC compared with placebo.[3] Gefitinib was also associated with a risk of severe drug-induced fatal interstitial lung disease (ILD),[4] which was later found to be a particularly high risk in Japanese patients.[5] Thus gefitinib was not recommended for use in Japan at this time.

The identification of *EGFR* somatic mutations changed the situation dramatically. Mutations such as exon 19 deletions and L858R in exon 21 in the *EGFR* coding domain identified in tumor specimens from patients with NSCLC who experienced a good response to gefitinib were revealed to cause excessive tumor growth by autophosphorylation of the EGFR downstream signal cascade.[6] The mutations highly linked with "oncogene addiction" were later recognized as "driver mutations", and pivotal pre-clinical research suggested that the blockade of EGFR signaling by specific TKIs caused a durable response of NSCLC with *EGFR* mutations.[7] This review examines the progress that has been made in EGFR-TKI treatment for *EGFR*-mutated NSCLC.

EGFR-TKI monotherapy for *EGFR*-mutated NSCLC

Soon after a retrospective report of a durable response to gefitinib in patients with *EGFR*-mutated

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NSCLC,[6] we conducted a small phase II study of gefitinib in Tohoku University Hospital. It was the first prospective study to evaluate the efficacy and safety of gefitinib as first-line treatment for advanced NSCLC with *EGFR* mutations. Mutations were identified by DNA direct sequencing before treatment commenced. At this time, concern had been raised about gefitinib treatment causing drug-induced ILD, which occurred more frequently among Japanese patients than in those from western countries.[5] However, the high effectiveness of the treatment for this population, including a response rate of 75% and a PFS of around 10 months, dispelled concerns from a risk–benefit balance viewpoint.[8] This marked the beginning of individualized treatment for advanced NSCLC. Another phase II study, NEJ001, conducted by the North-East Japan Study Group (NEJSG) reported that gefitinib monotherapy was highly effective with acceptable toxicities even for *EGFR*-mutated NSCLC patients with poor performance status (PS; 3–4) who had not been recommended for standard chemotherapy.[9] These results were described as the "Lazarus Response" in an editorial.[10]

Since our report, several phase II studies conducted in Japan have also demonstrated good results with gefitinib, and these were eventually combined into the I-CAMP study.[11] In this analysis, the combined data of patients treated with gefitinib were retrospectively compared with those of patients treated with standard platinum-based chemotherapy. Results suggested that gefitinib was superior to standard chemotherapy (median PFS of the gefitinib group and chemotherapy group, 10.7 and 6 months, respectively; $p < 0.001$). Based on these promising results of EGFR-TKI monotherapy, the NEJSG group conducted a multi-centered prospective phase III study, NEJ002, which compared gefitinib with standard chemotherapy (carboplatin [CBDCA] plus paclitaxel [PTX]) as the first-line treatment for advanced *EGFR*-mutated NSCLC. This used the highly sensitive peptide nucleic acid-locked nucleic acid PCR clamp method, developed by Dr. Hagiwara, to detect *EGFR* mutations from small samples such as sputum or effusions.[12] Enrolment in the study was successful due to the introduction of this PCR-based method, because sufficient tumor samples were often not obtained from patients with inoperable advanced NSCLC. NEJ002 revealed that gefitinib was significantly better than standard chemotherapy in terms of response rate, PFS, and quality of life (QOL).[13),14] Although the OS did not different between groups, this less toxic novel therapy was accepted as the new standard treatment for *EGFR*-mutated NSCLC. At the same time as NEJ002, another phase III study, I-PASS, compared gefitinib with CBDCA+PTX for advanced NSCLC patients with some favorable characteristics for EGFR-TKI such as adenocarcinoma histology and non/light smoking history. Subgroup analysis of I-PASS clearly showed that patient selection by *EGFR* mutation status was much better than by the abovementioned clinical features.[15]

Subsequently, the WJTOG3405 study reported the superiority of gefitinib compared with standard cisplatin plus docetaxel.[16] Similar comparative studies conducted outside Japan also demonstrated that gefitinib or erlotinib, another EGFR-TKI, were superior to standard chemotherapy; EGFR-TKI then became the new standard first-line treatment for advanced NSCLC patients with *EGFR* mutations (Table 1).[17),18] A few years later, afatinib and dacomitinib were developed as second-generation EGFR-TKIs capable of blocking signal cascades not only from EGFR (ErbB1) but also other ErbB families (ErbB2-4) irreversibly. Afatinib was revealed to be superior to standard chemotherapy with respect to PFS in two phase III studies, and dacomitinib demonstrated superiority to gefitinib regarding PFS and OS in the ARCHER study.[19)–21] Osimertinib, the third-generation EGFR-TKI that conquered a T790M-resistant mutation, an acquired gene mutation in tumors resistant to first- and second-generation EGFR-TKIs, was initially approved for *EGFR*-mutated NSCLC with T790M after the first- or second-generation EGFR-TKI treatment based on positive results of the AURA3 study.[22] Recently it also showed significant superiority to gefitinib and erlotinib with respect to PFS and OS as the first-line treatment for *EGFR*-mutated NSCLC in the FLAURA study.[23] Osimertinib has another advantage of being effective in brain metastasis.[24] Because osimertinib is less toxic than first-generation EGFR-TKIs regarding subjective adverse events such as skin rash, paronychia, and diarrhea, it is currently accepted as the new standard first-line treatment for *EGFR*-mutated advanced NSCLC.

Development of combined therapy with EGFR-TKI for *EGFR*-mutated NSCLC

Post-hoc analysis of NEJ002 revealed that more than 30% of patients treated with gefitinib as first-line treatment did not receive subsequent treatment with platinum agents, whereas 98% of patients

Table 1. Phase III studies of EGFR-TKI monotherapy as the first-line treatment for *EGFR*-mutated NSCLC

Name of study[reference] (number of patients)	EGFR-TKI Compared treatment	RR (%)	PFS (m)	HR (95%CI) p value	OS (m)	HR (95%CI) p value
IPASS (subgroup analysis)[14]	gefitinib	71	9.5	0.48 (0.36–0.64)	18.6	0.91 (0.76–1.10)
(n = 261)	CBDCA+PTX	47	6.3	<0.001	17.3	NA
NEJ002[13]	gefitinib	74	10.8	0.30 (0.22–0.41)	27.7	0.89 (0.63–1.24)
(n = 230)	CBDCA+PTX	31	5.4	<0.001	26.6	NA
WJTOG3405[16]	gefitinib	62	9.2	0.49 (0.34–0.71)	36.5	1.19 (0.77–1.83)
(n = 172)	CDDP+DOC	32	6.3	<0.0001	36.8	NA
OPTIMAL[17]	erlotinib	83	13.7	0.16 (0.11–0.26)	22.7	1.04 (0.69–1.58)
(n = 165)	CBDCA+GEM	36	4.6	<0.0001	28.9	NA
EURTAC[18]	erlotinib	61	9.7	0.37 (0.25–0.54)	19.3	1.04 (0.65–1.68)
(n = 174)	platinum-doublet	18	5.2	<0.0001	19.5	NA
LUX-Lung3[19]	afatinib	61	13.6	0.47 (0.34–0.65)	28.2	0.88 (NA)
(n = 345)	CDDP+PEM	22	6.9	<0.0001	28.2	0.385
LUX-Lung6[20]	afatinib	74	11.0	0.28 (0.20–0.39)	23.1	0.93 (NA)
(n = 363)	CDDP+GEM	31	5.6	<0.0001	23.5	0.6137
ARCHER[21]	dacomitinib		14.7	0.59 (0.47–0.74)	34.1	0.760 (0.582–0.993)
(n = 452)	gefitinib		9.2	<0.0001	26.8	0.044
FLAURA[23),29]	osimertinib	80	18.9	0.46 (0.37–0.57)	38.6	0.799 (0.641–0.997)
(n = 556)	gefitinib or erlotinib	76	10.2	<0.0001	31.8	0.0462

RR, response rate; PFS, progression-free survival; HR, hazard ratio; CI, confidence interval; OS, overall survival; CBDCA, carboplatin; PTX, paclitaxel; CDDP, cisplatin; DOC, docetaxel; GEM, gemcitabine; PEM, pemetrexed; NA, not available.

treated with first-line chemotherapy received gefitinib; this was one reason why the first-line gefitinib group did not improve their OS compared with the first-line chemotherapy group.[25] The analysis also suggested that patients who received EGFR-TKI, platinum agents, and pemetrexed (PEM; a novel standard agent for non-squamous NSCLC) achieved a longer OS than those who received EGFR-TKI and platinum agents without PEM. Thus, we hypothesized that "using up" these important three key drugs (EGFR-TKI, platinum agents, and PEM) may improve the OS of patients with *EGFR*-mutated NSCLC.

NEJ005, a randomized phase II study that compared two different schedules of EGFR-TKI and chemotherapy combination, was initiated in 2010. It demonstrated similar efficacies for both the concurrent group (gefitinib, CBDCA, and PEM concurrently) and the alternating group (2 cycles of alternating gefitinib alone and chemotherapy with CBDCA plus PEM followed by PEM alone every 8 weeks) with response rates and PFS of 88% and 18.3 months and 85% and 15.3 months, respectively. Safety levels as measured by the incidence of ≥grade 3 toxicities were similar between groups and there were no treatment-related deaths in either group.[26] Moreover, the OS was longer in the concurrent group and the schedule because this was much easier in general practice; therefore, we selected the concurrent regimen for an experimental treatment in a subsequent large phase III study, NEJ009.[27]

NEJ009 was the first phase III trial that compared a combination regimen with EGFR-TKI and chemotherapy with EGFR-TKI alone for untreated advanced NSCLC with *EGFR* mutations. In this trial, the combination group demonstrated a significantly longer PFS and OS than the gefitinib monotherapy group (Table 2).[27] Although the overall frequency of toxicities in the combination group was more than in the monotherapy group, the frequency of treatment-related severe toxicities and treatment discontinuation caused by toxicity did not differ, and neither did the QOL evaluation. At a similar time to the NEJ009 report, another phase III study conducted in India compared the same regimens for *EGFR*-mutated NSCLC, and also found that the combination regimen was superior to gefitinib alone.[28] Additionally, the latest OS analysis from the FLAURA study reported an MST for first-line osimertinib (the current global standard) of 38.8 months.[29] Based on the above evidence, a strategy of recommending the NEJ009 regimen for patients with

Table 2. Phase III studies of combined regimen with EGFR-TKI as the first-line treatment for *EGFR*-mutated NSCLC

Name of study[reference] (number of patients)	Combined regimen Compared treatment	RR (%)	PFS (m)	HR (95%CI) p value	OS (m)	HR (95%CI) p value
EGFR-TKI combined with cytotoxic agents						
NEJ009[27]	gefitinib+CBDCA+PEM	71	20.9	0.49 (0.39–0.62)	50.9	0.72 (0.55–0.95)
(n = 345)	gefitinib	47	11.2	<0.001	38.8	0.021
Noronha's study[28]	gefitinib+CBDCA+PEM	74	16	0.51 (0.39–0.66)	NR	0.45 (0.31–0.65)
(n = 350)	gefitinib	31	8	<0.0001	17	<0.0001
EGFR-TKI combined with anti-angiogenic agent						
NEJ026[30]	erlotinib+bevacizumab	61	16.9	0.605 (0.417–0.877)	28.2	0.88
(n = 228)	erlotinib	22	13.3	0.016	28.2	0.385
RELAY[31]	erlotinib+ramucirumab	74	19.4	0.591 (0.461–0.760)	NR	0.83 (0.53–1.30)
(n = 449)	erlotinib	31	12.4	<0.0001	NR	NA

RR, response rate; PFS, progression-free survival; HR, hazard ratio; CI, confidence interval; OS, overall survival; CBDCA, carboplatin; PEM, pemetrexed; NR, not reached; NA, not available.

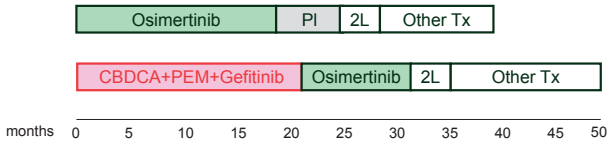

Fig. 1. Current treatment strategy for *EGFR*-mutated advanced NSCLC. A sequence of first-line osimertinib followed by platinum-based chemotherapy (Pl), and second-line chemotherapy (2L) such as docetaxel and other treatments (Tx) including best supportive care alone, which demonstrated overall survival of around 38 months, is recommended for patients who prefer a less toxic standard regimen (upper line). Another sequence with the first-line NEJ009 regimen including carboplatin (CBDCA), pemetrexed (PEM), and gefitinib followed by osimertinib (only available when T790M mutation was detected), 2L, and other Tx had the potential to achieve an overall survival of around 50 months and is recommended for patients with good performance status (lower line). The length of each bar in the figure indicates PFS presented in previous phase III studies such as AURA3 (second-line osimertinib) or FLAURA (first-line osimertinib).

a good PS who can tolerate enhanced toxicities to achieve a longer OS could be reasonable. Although osimertinib is still appropriate for patients who prefer a less toxic regimen, especially those with a poor PS and/or symptomatic brain metastases (Fig. 1).

Another combination with EGFR-TKIs and an anti-angiogenic agent has also been investigated. Based on promising results from a randomized phase II study, a combination regimen with erlotinib and bevacizumab, a humanized anti-vascular endothelial growth factor (VEGF) monoclonal antibody that binds and neutralizes all human VEGF-A isoforms and bioactive proteolytic fragments, was compared with erlotinib alone in a phase III trial, NEJ026. This showed that the combination regimen achieved a significantly longer PFS than erlotinib alone.[30] Additionally, the RELAY study that compared a combination of erlotinib and ramucirumab, a human monoclonal IgG1 antibody that selectively targets VEGFR2, demonstrated that the combination regimen also achieved a significantly longer PFS than erlotinib alone (Table 2).[31] Although these combinations are promising treatments for *EGFR*-mutated NSCLC, the OS results are still immature, so their clinical benefit is currently unclear.

Future perspectives of treatments for *EGFR*-mutated NSCLC

There are some clinical questions regarding treatments with EGFR-TKI for *EGFR*-mutated NSCLC. First, because no direct comparison between osimertinib and the NEJ009 regimen has been carried out, the true superiority is unknown. Although patient selection considering the risk–benefit balance is recommended, further evidence is awaited. Second, the benefit of a promising combination of osimertinib and chemotherapy is still unknown, although this should be elucidated by the ongoing FLAURA2 phase III study comparing a combination of osimertinib with CBDCA and PEM to osimertinib alone (NCT04035486).[32] Third, the usefulness of immune checkpoint inhibitors for *EGFR*-mutated NSCLC is also unknown. Although a subgroup analysis of the IMPOWER150 study suggested that a combination regimen with atezolizumab, CBDCA, paclitaxel, and

bevacizumab was effective for *EGFR*-mutated NSCLC, prospective validation of this is urgently needed.[33] By overcoming these problems, it is expected that therapy for *EGFR*-mutated NSCLC will be further improved.

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Profile

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