

Toxicity profile of epidermal growth factor receptor tyrosine kinase inhibitors in patients with epidermal growth factor receptor gene mutation-positive lung cancer (Review)

MASAYUKI TAKEDA and KAZUHIKO NAKAGAWA

Department of Medical Oncology, Kinki University Faculty of Medicine, Osaka-Sayama, Osaka 589-8511, Japan

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Abstract. Recent progress in the research on the molecular biology of lung cancer revealed that the clinical response to epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) is associated with the presence of activating *EGFR* mutations. Three EGFR-TKIs, namely afatinib, erlotinib and gefitinib, are currently available for the treatment of patients with *EGFR* mutation-positive non-small-cell lung cancer (NSCLC). Due to the dearth of published phase III trials prospectively evaluating the effects of one EGFR-TKI in comparison with another in such patients, the decision-making regarding which agent to recommend to any given patient lies with the treating physician. Given the potential long-term exposure of such patients to EGFR-TKIs, the toxicological properties of these drugs in such patients may differ from those observed in unselected patients. The aim of the present study was to provide an overview of the key adverse events (rash, diarrhea, hepatotoxicity and interstitial lung disease) reported for EGFR-TKIs in clinical trials including patients with advanced NSCLC.

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Correspondence to: Dr Masayuki Takeda, Department of Medical Oncology, Kinki University Faculty of Medicine, 377-2 Ohno-higashi, Osaka-Sayama, Osaka 589-8511, Japan
E-mail: takedamasa2004@yahoo.co.jp

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1. Introduction

Recent progress in the research on the molecular biology of lung cancer has led to the identification of oncogenic drivers, such as mutation of the epidermal growth factor receptor (EGFR) gene and translocation of the anaplastic lymphoma kinase (ALK) gene (1-5). The discovery that activating mutations of *EGFR* are associated with a marked response to the EGFR tyrosine kinase inhibitor (TKI) gefitinib in patients with non-small-cell lung cancer (NSCLC) led to the undertaking of several randomized phase III studies to compare EGFR-TKIs with platinum doublets in patients with *EGFR* mutation-positive NSCLC (6-11). The results of these trials confirmed the superiority of EGFR-TKI treatment over standard chemotherapy in terms of progression-free survival (PFS) in these biomarker-selected patients. Three EGFR-TKIs, namely gefitinib, erlotinib and afatinib, are currently available for the first-line therapy of patients with advanced NSCLC positive for *EGFR* mutations. However, there have been no published phase III trials that have prospectively evaluated the effects of one EGFR-TKI in comparison with another in such patients. The decision to recommend to a patient one EGFR-TKI over another therefore lies with the treating physician in clinical practice. Differences in safety among these three EGFR-TKIs have been identified and may affect treatment-related decisions. Given the potential long-term exposure of biomarker-selected patients to EGFR-TKIs, however, the toxicological properties of these agents in such patients may differ from those observed in unselected patients. The aim of this review was to provide an overview of key adverse events, such as rash, diarrhea, hepatotoxicity and interstitial lung disease (ILD), reported for EGFR-TKIs in clinical trials that were largely restricted to patients with *EGFR* mutation-positive tumors.

2. Pooled safety data from prospective trials for *EGFR* mutation-positive NSCLC

To the best of our knowledge, no randomized phase II or III trials performing a prospective evaluation of the efficacy and safety of one EGFR-TKI in comparison with another in patients with *EGFR* mutation-positive NSCLC had been fully published by early 2015. Therefore, a pooled safety analysis of the incidence of severe (grade ≥ 3) toxicity according to the type of EGFR-TKI administered was undertaken, using data

Table I. Frequency (%) of grade ≥ 3 adverse events according to the type of EGFR-TKI.

Adverse event	WJOG 5108L (72% <i>EGFR</i> mutation-positive)		LUX-Lung 7 (all <i>EGFR</i> mutation-positive)	
	Erlotinib	Gefitinib	Gefitinib	Afatinib
Hepatotoxicity ^a	3.3/2.2	13.0/6.1	8.2/2.5	0/0
Rash	18.1	2.2	3.1	9.4
Diarrhea	3.3	2.2	1.3	12.5
ILD	1.4	0.4	2.5 (all grades)	0

^aIncrease in circulating ALT/AST levels. EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; ILD, interstitial lung disease; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

extracted from prospective clinical trials including advanced NSCLC patients harboring *EGFR* mutations (12). A search through the PubMed database identified 21 phase II or III trials of EGFR-TKIs including such patients. The incidence of grade ≥ 3 liver toxicity was significantly higher in gefitinib-treated patients compared with that in patients treated with erlotinib (18 vs. 5.4%, respectively), as well as in erlotinib-treated patients compared with that in patients treated with afatinib (5.4 vs. 1.7%, respectively). The frequency of grade ≥ 3 rash was higher among afatinib-treated patients compared with that among those treated with erlotinib (15 vs. 8.8%, respectively), as well as among erlotinib-treated patients compared with those treated with gefitinib (8.8 vs. 3.5%, respectively). Grade ≥ 3 diarrhea occurred more frequently in afatinib-treated patients compared with those treated with erlotinib (9.6 vs. 2.7%, respectively), whereas the frequency of this toxicity did not differ significantly between patients treated with erlotinib and those receiving gefitinib (2.7 vs. 1.1%, respectively). Although ILD is rare, it is potentially fatal; thus, we also assessed the frequency of this toxicity at grade ≥ 3 and found that its incidence did not differ significantly among the three groups of patients (2.2% for gefitinib vs. 0.6% for erlotinib or afatinib). Therefore, there were clinically significant differences in the occurrence of hepatotoxicity, rash and diarrhea among patients treated with these three EGFR-TKIs, although such differences have been directly investigated in only a limited number of patients to date.

3. Afatinib vs. gefitinib (LUX-Lung 7)

Early results have been reported for a randomized, open-label phase IIb trial of afatinib vs. gefitinib as first-line treatment for patients with advanced lung adenocarcinoma who were positive for exon 19 deletions or the L858R point mutation of *EGFR* (LUX-Lung 7, ClinicalTrials.gov identifier NCT 01466660) (13). The primary endpoint of this study was to compare afatinib with gefitinib in terms of PFS, overall survival (OS) and time to treatment failure. A total of 571 patients were screened, 319 of whom were randomized to either the afatinib (n=160) or gefitinib (n=159) arms. Afatinib treatment was associated with a significantly improved PFS [median, 11.0 vs. 10.9 months; hazard ratio (HR)=0.73,

P=0.0165], time to treatment failure (median, 13.7 vs. 11.5 months; HR=0.73, P=0.0073) and objective response rate (70 vs. 56%, P=0.0083) compared with gefitinib. Treatment with either drug was generally tolerable, resulting in equally low rates of treatment-related discontinuation in the two arms (6.3%). The frequency of grade ≥ 3 diarrhea (12.5 vs. 1.3%) and rash or acne (9.4 vs. 3.1%) was higher in the afatinib arm compared with that in the gefitinib arm, whereas the frequency of a grade ≥ 3 increase in the circulating levels of alanine aminotransferase (ALT)/aspartate aminotransferase (AST) was higher with gefitinib compared with afatinib (8.2/2.5 vs. 0/0%) (Table I). Drug-related ILD was reported in 4 patients on gefitinib and none on afatinib. These results are thus consistent with those of our pooled analysis, demonstrating that grade ≥ 3 rash or diarrhea occur more frequently among patients treated with afatinib, whereas hepatotoxicity is more frequent among those treated with gefitinib.

4. Erlotinib vs. gefitinib (WJOG 5108L trial)

A multicenter, randomized phase III study was designed to demonstrate the non-inferiority of gefitinib to erlotinib for advanced lung adenocarcinoma (WJOG 5108L, UMIN000002014) (14). Previously treated patients were randomized in a 1:1 ratio to receive either erlotinib (150 mg daily) or gefitinib (250 mg daily) according to gender, disease stage, *EGFR* mutation status, performance status, smoking history, line of chemotherapy and institution. The protocol was amended in December, 2011, as the Pharmaceuticals and Medical Devices Agency of Japan limited the use of gefitinib to patients harboring *EGFR* mutations. A total of 561 patients were accrued, 2 of whom proved to be ineligible; finally, 280 and 279 subjects were randomly assigned to the erlotinib and gefitinib arms, respectively, including 198 (70.7% in the erlotinib arm) and 203 (72.8% in the gefitinib arm) with tumors positive for activating mutations of *EGFR*. The median PFS was 6.5 and 7.5 months (HR=1.125, P=0.257) and the median OS was 22.8 and 24.5 months (HR=1.038, P=0.768) for gefitinib and erlotinib, respectively. The median PFS in patients harboring *EGFR* mutations was 8.3 and 10.0 months (HR=1.093, P=0.424) for gefitinib and erlotinib, respectively. The study did not demonstrate non-inferiority of gefitinib compared with erlotinib in terms of PFS in patients with

lung adenocarcinoma according to the predefined criteria. The incidence of grade ≥ 3 rash was higher in the erlotinib arm compared with that in the gefitinib arm (18.1 vs. 2.2%, respectively), whereas that of grade ≥ 3 diarrhea did not differ significantly between the erlotinib and gefitinib arms (3.3 vs. 2.2%, respectively) (Table I). A grade ≥ 3 increase in ALT/AST was more frequent with gefitinib compared with erlotinib (13.0/6.1 vs. 3.3/2.2%, respectively). A 4% incidence of ILD of any grade was reported in each group, with 3 patients in the erlotinib arm experiencing grade 5 ILD. Thus, there was a significant difference in the frequencies of rash and hepatotoxicity between the two treatment arms, although the toxicity profile for this trial may not accurately represent that for a homogeneous *EGFR* mutation-positive population, given that only 72% of the trial patients harbored such mutations.

5. Mechanisms underlying safety differences among EGFR-TKIs

EGFR-TKI-induced rash and diarrhea are usually mild to moderate in severity. The frequency of these adverse events at grade ≥ 3 appears to be higher among patients treated with afatinib compared with those treated with gefitinib. These differences may be explained in part by the mechanism of drug action. EGFR is expressed in epithelia and helps to maintain mucosal integrity and to promote mucosal repair in the gut, as well as to maintain the protective barrier of the skin. Afatinib exhibits a higher affinity for the kinase domain of EGFR compared with gefitinib, and the irreversible tyrosine kinase blockade mediated by afatinib may result in more sustained suppression of EGFR signaling compared with that induced by the reversible inhibitor gefitinib (15). However, the frequency of grade ≥ 3 rash appears to be higher among patients treated with erlotinib compared with those treated with gefitinib, with this difference possibly being attributable to a difference in pharmacological properties between the two drugs. Administration of erlotinib at the maximum tolerated and approved dose of 150 mg once daily thus gives rise to a steady-state plasma trough concentration that is ~ 3.5 times that for gefitinib administered at the recommended dose (\sim one-third of the maximum tolerated dose) of 250 mg once daily (16,17).

The reason for liver dysfunction being more frequent among patients treated with gefitinib compared with those receiving other EGFR-TKIs remains unclear. A previous study evaluated the frequency of adverse events according to the functional status of CYP2D6, an enzyme that mediates the metabolism of gefitinib, in unselected patients treated with gefitinib or erlotinib (18). That study demonstrated that reduced CYP2D6 function was associated with an increased risk of rash, but not of liver dysfunction, in the gefitinib cohort, suggesting that the hepatotoxicity of gefitinib may not be dose-dependent. Another study investigated the association of polymorphisms of the CYP2D6 gene with gefitinib hepatotoxicity and found that gene variants associated with reduced CYP2D6 activity were not predictive of hepatotoxicity (19). A case series study demonstrated that erlotinib was effective and well-tolerated as a treatment option following discontinuation of gefitinib as a result of drug-related hepatotoxicity (20). Erlotinib and gefitinib share a 4-anilinoquinazoline base structure, but they differ in the substituents attached to the quinazoline and anilino

rings. Minor differences in the chemical structures of these compounds may thus affect hepatotoxicity.

6. Conclusions

The application of the EGFR-TKIs gefitinib, erlotinib and afatinib have improved the clinical outcome of patients with *EGFR* mutation-positive NSCLC, but these agents are associated with a number of serious adverse events that require management. The safety profile of different EGFR-TKIs should be taken into consideration by the treating physician when selecting the most appropriate drug with regard to mitigation of the risk for certain types of toxicity.

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