Original Article

Does dose reduction of afatinib affect treatment outcomes of patients with *EGFR*-mutant metastatic non-small cell lung cancer in real-world clinical practice?

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Background: Afatinib can be started at a dose lower than the recommended starting dose of 40 mg/day for the treatment of epidermal growth factor receptor (*EGFR*)-mutant non-small cell lung cancer (NSCLC), however treatment outcomes in real-world clinical practice remains unclear.

Methods: This retrospective study of patients with NSCLC from 18 major hospitals (public, private or university teaching hospitals) enrolled in Malaysia's National Cardiovascular and Thoracic Surgical Database (NCTSD) assessed the efficacy of lower doses of afatinib on treatment outcomes in a real-world clinical practice. Data on clinical characteristics, afatinib dosing, and treatment outcomes for patients included in NCTSD from 1st January 2015 to 31st December 2020 were analyzed.

Results: Of the 133 patients studied, 94.7% had adenocarcinoma. Majority of the patients (60.9%) had *EGFR* exon 19 deletion and 23.3% had *EGFR* exon 21 L858R point mutation. The mean age of patients was 64.1 years and majority (83.5%) had Eastern Cooperative Oncology Group performance status of 2–4 at diagnosis. The most common afatinib starting doses were 40 mg (37.6%), 30 mg (29.3%), and 20 mg (26.3%) once daily (OD), respectively. A quarter of patients had dose reduction (23.3%) due to side effects or cost constraints. Majority of the patients had partial response to afatinib (63.2%) whilst 2.3% had complete response. Interestingly, the objective response rate was significantly higher (72.3%) with afatinib OD doses of less than 40 mg compared to 40 mg (54.0%) (P=0.032). Patients on lower doses of afatinib were two times more likely to achieve an objective response [odds ratio =2.64; 95% confidence interval (CI): 1.20–5.83; P=0.016]. These patients had a numerically but not statistically longer median time to treatment failure (TTF). Median TTF (95% CI) for the overall cohort was 12.4 (10.02–14.78) months. Median overall survival (95% CI) was 21.30 (15.86–26.75) months.

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Conclusions: Lower afatinib doses (<40 mg OD) could be equally effective as standard dose in patients with *EGFR*-mutant advanced NSCLC and may be more suited to Asian patients, minimizing side effects that may occur at higher dosages of afatinib leading to dose interruptions and affecting treatment outcomes.

Keywords: Adenocarcinoma; resource-limited settings; survival; treatment outcome; tyrosine kinase inhibitors (TKIs)

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Introduction

In 2020, the World Health Organization (WHO) estimated that globally, lung cancer was the second most common cancer (2.21 million cases) and the leading cause of cancer death (1.80 million deaths) (1). In Malaysia, 5,139 new cases of lung cancer were reported in 2020, which was 10.2% of all cancers in the country for that year (2). The 1-year survival rates of patients with lung cancer in Malaysia between 2007 and 2016 were 63.3% for stage I disease and 29.6% for stage IV disease (3). The 5-year survival rates were 37.1% for stage I disease and 6.3% for stage IV disease (3). Majority of lung cancer cases are non-small cell lung cancer (NSCLC) (4,5). Patients with NSCLC harboring epidermal growth factor receptor (*EGFR*) mutations are common, with Asian patients having a higher rate of *EGFR* mutation (*EGFR*m+) than Caucasians (6).

The recommended first-line treatment for *EGFR*m+ NSCLC is an EGFR tyrosine kinase inhibitor (TKI) (7,8). Afatinib, an irreversible second generation EGFR TKI, has activity against common as well as rare *EGFR* mutations (9). Two major randomized controlled phase III trials (the global LUX-Lung 3 and the Asian LUX-lung 6 trials) demonstrated afatinib's efficacy in *EGFR*m+ NSCLC patients with significant improvements in progression-free survival (PFS) and overall survival (OS) versus chemotherapy (10-12). In another major trial, patients on afatinib had significantly longer PFS and time to treatment failure (TTF) compared to gefitinib, a first generation EGFR TKI (13,14).

The recommended starting dose of afatinib is 40 mg/day, which can be reduced if there are adverse reactions (15). Evidence from clinical trials and real-world clinical practice showed that with dose adjustments, adverse events (AEs) associated with afatinib can be managed safely (16). In one study, maintenance doses of afatinib at 40 or 30 mg once daily (OD) were effective and tolerable for Malaysian patients with *EGFR*m+ NSCLC (17).

The objective of this retrospective study was to assess the efficacy of lower doses of afatinib on treatment outcomes in patients with *EGFR*m+ NSCLC in real-world clinical practice. We present this article in accordance with the STROBE reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-23-691/rc).

Highlight box

Key findings

- Patients with epidermal growth factor receptor (*EGFR*)-mutant non-small cell lung cancer (NSCLC) in real-world clinical practice on afatinib doses of less than 40 mg once daily (OD) had significantly higher objective response rate (72.3%) compared to those on 40 mg OD (54.0%) (P=0.032).

What is known and what is new?

- Afatinib is effective for patients with *EGFR*-mutant advanced NSCLC.
- Low dose afatinib could be equally effective as standard dose in these patients.

What is the implication, and what should change now?

- Individualized titration of dosage of afatinib is recommended to optimize the balance of risk and benefit.

Methods

Study design and data source

This was a retrospective, observational study of adult patients (18 years or older) with stage IIIB, IIIC and IV (8th edition AJCC) NSCLC who received standard of care treatment following international guidelines. The patients were identified from the National Cardiovascular and Thoracic Surgical Database (NCTSD) between 1st January 2015 and 31st December 2020. Patients with incomplete