

EDITORIAL

3rd Generation EGFR TKIs – A Major Breakthrough for NSCLC Treatment

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ABSTRACT

Dengue is an important tropical arboviral infection. The lung disease in dengue is limited mentioned. In this short, editorial, lung disease in dengue is summarized, detailed and discussed.

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Key words: EGFR; EGFR Mutation; TKI; T790M Mutation; C01686; AZ9291

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EDITORIAL

In 1986 Stanley Cohen won the Nobel Prize for his discovery of the epidermal growth factor (EGF)^[1]. Its receptor was isolated in 1988 when Mendelsohn and colleagues first suggested EGFR as an anticancer agent^[2]. But it was not until May 2004 when 2 pivotal studies revealed the correlation between somatic mutations in the kinase domain of EGFR and the strong response of advanced NSCLC to EGFR tyrosine kinase inhibitors (TKIs)^[3,4].

It is well established that 10- 15% of lung adenocarcinomas diagnosed in the United States harbour activating mutations in the EGFR gene^[5]. The remarkable efficacy of small molecule EGFR TKIs in this unique subset of patients has revolutionized the therapeutic approach to lung cancer and created a treatment paradigm for other molecular defined subsets of cancer. Multiple randomized phase 3 studies have demonstrated that EGFR TKIs are superior to chemotherapy in patients with stage IV EGFR- mutated disease, with excellent response rates (58-75%) and progression- free survival^[6-8]. Thus, first generation EGFR TKIs such as erlotinib, gefitinib are now standard first- line therapy for advanced non- small cell lung cancer (NSCLC) with sensitising EGFR mutations. Second generation EGFR TKIs (afatinib, dacomitinib) with covalent irreversible binding to the receptor and with the potential to target heterodimers of the Erb-B receptors gave further promise regarding response, progression free survival and overall survival, particularly in patients with exon 19 deletions^[9-11].

This unprecedented success of these agents logically leads to clinical questions:

- Is this therapy enough to achieve long –term remission and cure?
- Are new generation EGFR TKIs better as first line treatment?
- Are EGFR TKIs beneficial in earlier stages of disease?

Although significant improvement in clinical outcomes has been achieved with these agents no reports of definitive treatment exist main reason being the development of acquired resistance (AR). Different mechanisms have been responsible for AR including secondary EGFR mutation (predominantly T790M), activation of parallel or downstream signalling pathways, phenotypic transformation such as epithelial to mesenchymal transition (EMT) and small cell lung (SCLC) transformation. The most common type of AR is mutation in codon 790 (T790M) in EGFR exon 20, which accounts for 50-60% of cases with AR to gefitinib/erlotinib^[12].

In April 2015 two articles were published in the New England Journal of Medicine describing the use of third generation EGFR TKIs (AZ9291 and C01686) in patients with NSCLC and EGFR-sensitising mutations progressing under first or second generation

TKIs^[8, 13]. Both substances were targeting the T790M mutation and the trials were similar in design with a conventional phase I part followed by an extension cohort at a predefined dose.

C01686 (Rociletinib) is a third- generation TKI targeting the T790M mutation. This study demonstrated an overall response rate (ORR) OF 59% in T790M – mutant patients and 29% in non T790M-mutant. The study included 130 patients but ORR is reported in 92, including 46 with the T790M mutation. The estimated median progression-free survival (PFS) is 13.1 months for patients with the mutation and 5.6 in those without it. Two different galenic forms of the drugs were tested sequentially, first a free-base form at dose up to 900mg twice a day, then a hydrogen bromide salt form designed to improve pharmacokinetics at doses between 500-1000mg twice daily. The main side effect in this trial was hyperglycaemia, affecting 22 % of cases and requiring dose reduction and antiglycaemic medication. Asymptomatic QT prolongation was also reported and other adverse effects like diarrhoea, rash, and fatigue were rare and mild. 48% of patients required dose reduction.

The second study published in New England Journal of Medicine evaluated the AZ9291 in 253 patients with NSCLC and T790M mutation. It demonstrated an ORR of 51%, including 61% of ORR in T790M mutation population and only 21% in no T790M mutation. Similarly PFS was 9.6 months and 2.8 months respectively. The dose was 80mg once daily and was well tolerated with frequent side effects including diarrhoea, skin rash and nausea.

In conclusion third generation EGFR TKIs have demonstrated excellent and promising results in patients having developed acquired resistance through a T790M mutation. Patient selection remains extremely important and identification of the mechanism for acquired resistance is the key for the use of appropriate EGFR TKI. Further trials are necessary to compare these promising agents with already existing chemotherapy regimens to define optimal sequence of use.

CONFLICT OF INTERESTS

The authors have no conflicts of interest to declar.

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