The relationship between BIM deletion polymorphism and clinical significance of epidermal growth factor receptor-mutated non-small cell lung cancer patients with epidermal growth factor receptor-tyrosine kinase inhibitor therapy: a meta-analysis

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Background: BIM deletion polymorphism is a germline that might lead to little or no BH3 expression, which affects epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKI) related apoptosis. Recent studies show that BIM deletion polymorphism might be a critical factor leading to the resistance of EGFR-TKIs in EGFR mutation-positive non-small cell lung cancer (NSCLC) patients.

Methods: Thus, a meta-analysis was conducted by combing seven original eligible studies including 778 NSCLC patients to investigate a steady and reliable conclusion.

Results: Our study indicated that BIM deletion polymorphism was significantly associated with the poor objective response rate (ORR) of EGFR-TKIs in EGFR-mutated NSCLC patients [odds ratios (OR) = 0.55, 95% confidence interval (CI), 0.33-0.92]. And disease control rate (DCR) in EGFR-mutate NSCLC patients treated with EGFR-TKIs was significantly decreased in patients with BIM deletion polymorphism (OR = 0.55, 95% CI, 0.27-1.12). Moreover, the progression-free survival (PFS) of patients with BIM deletion polymorphism is shorter.

Conclusions: These findings suggested that BIM deletion polymorphism might be a genetic cause of intrinsic resistance to TKI therapy and it could be emerged as an independent predictor to identify patients who would benefit from TKI targeted therapy in EGFR-mutated NSCLC.

Keywords: BIM; polymorphism; epidermal growth factor receptor (EGFR); tyrosine kinase inhibitors (TKIs); non-small cell lung cancer (NSCLC)

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Introduction

Lung cancer is the most common morbidity and mortality cancer all over the world. About 89% of lung cancer patients are non-small cell lung cancer (NSCLC) (1), and when patients were diagnosed as NSCLC, most lost chance to have surgery or radical resection, the only treatment is chemotherapy which only can extend a little time to live and the side effects are critical (2). When the epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) such as gefitinib and erlotinib come out, the NSCLC patients who have an activating mutation of the EGFR gene have a new method to treatment, which can longer progression-free survival (PFS) than did those who received platinum-based chemotherapy, while also improving quality...
of life (3). However, the efficacy of EGFR TKIs cannot stay for long, about 10 to 16 months to develop a recurrence (4). The mechanism of resistance to EGFR-TKIs is not sure, it includes the acquisition of the T790M gatekeeper mutation, kinase switching due to mesenchymal-epithelial transition (MET) amplification, phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha (PIK3CA) mutation, and transformation into small-cell lung cancer (5-7).

B-cell lymphoma-2-like 11 gene (BIM), a member of the B-cell lymphoma-2 (Bcl-2) family genes, encodes BCL-2 interaction mediator of cell death protein (BIM), which is a critical modulator in promoting cell apoptosis (8). The impaired expression of pro-apoptotic BCL2-homology domain 3 (BH3) because of a 2903-bp germline deletion polymorphism of BIM, can be considered as an impossible factor cause the resistance of EGFR TKIs in EGFR-mutated NSCLC patients (9).

Materials and methods

The studies were found on PubMed and the Web of Science databases dating up to July, 2015. The searching key words include “BIM deletion polymorphism”, “EGFR-TKI and BIM”, and “EGFR-TKI and polymorphism”. Study selection was based on an initial screening of identified abstracts or titles and a second screening of full-text articles. Eligible studies were identified from relevant full-text study in accordance with the following inclusion criteria: (I) the study focus on BIM deletion polymorphism and EGFR-TKI treatment; (II) patients must be detected to find whether have BIM deletion polymorphism; (III) the patients in the study must have EGFR-mutate and receive EGFR-TKIs as a major treatment; (IV) studies quantified outcomes with adjusted odds ratios (OR), relative risk (RR), hazard ratio (HR), or number of events and corresponding 95% confidence intervals (CIs); (V) published full text available.

OR, HR, and 95% CI was used as common measurements for evaluating the strength between BIM deletion polymorphism and survival as well as response to EGFR-TKI therapy in lung cancer patients. All calculations were performed using Revman5.3 (The Nordic Cochrane Centre, the Cochrane Collaboration, Copenhagen, Denmark).

Results

A total of 159 relevant studies were retrieved and searched in the databases and manual retrieval. A total of 41 duplicated articles; 103 unrelated articles; and eight reviews, letter, or no data including were excluded from the present study in accordance with inclusion and exclusion criteria. As a result, seven eligible studies concerning BIM polymorphism and clinical response and outcome of EGFR-mutated NSCLC with EGFR-TKI treatment were selected in the meta-analysis (10-15). The flow chart of eligible study search was shown in Figure 1.

The relationship between BIM deletion polymorphism and the clinical outcome of EGFR-TKI in EGFR-mutated NSCLC patients were evaluated by combing with four original studies. Significant association was found between BIM deletion polymorphism and efficacy of EGFR-TKI treatment in patients (OR =0.55, 95% CI, 0.33–0.92) (Figure 2). And the disease control rate (DCR) in patients with BIM deletion polymorphism was decreased compared with patients without BIM deletion polymorphism (OR =0.55, 95% CI, 0.27–1.12) (Figure 3).

Six eligible studies reported association between BIM deletion polymorphism and PFS in EGFR-TKIs treated NSCLC patients. And the result was showed in Table 1.
The PFS of patients with BIM deletion polymorphism was shorter than those patients with BIM wild type.

Results of Begg’s funnel plot showed that no significant publication bias was found between objective response rate (ORR), DCR, and BIM polymorphism, respectively. There was no significant publication bias in comparison of BIM deletion and BIM wild type in ORR and DCR (Figure 4).

Discussion

EGFR-TKIs have been a new treatment on NSCLC patients with EGFR mutation, which can longer patients living time and decrease the side effects. However, a large number of NSCLC patients harbored EGFR mutation displayed primary resistance to EGFR-TKIs (6). BIM deletion polymorphism is a germline that affects EGFR-
TKI related apoptosis, which might lead to less or no BH3 expression. Therefore, a common deletion polymorphism within BIM was deemed as a candidate genetic cause of intrinsic resistance to kinase inhibitor therapy in these malignancies (10).

In order to make out the relationship between BIM deletion polymorphism and the clinical outcome in EGFR-mutated NSCLC patients received EGFR-TKIs, a meta-analysis was conducted by combing the data of eligible studies. Our results indicated that BIM deletion polymorphism contributed to a lower ORR and DCR in NSCLC patients than patients with BIM wild type treated with EGFR-TKIs. In addition, EGFR-mutated NSCLC patients who harbored BIM deletion polymorphism had a short PFS as compared to patients with BIM wildtype, showing that BIM deletion polymorphism may be a poor prognostic factor for EGFR-mutated NSCLC patients with EGFR-TKIs therapy. The deletion polymorphism is a 2,903 bp fragment deletion locus which is located in intron 2 and its frequency is only in Asian population, but absent in African and North American populations (10,16,17). BIM upregulation is required for TKIs to induce apoptosis in kinase-driven cancers through encoding a BH3-only protein which is a BCL2 family member (18). The BH3-only protein activated cell death by opposing the prosurvival members of the BCL2 family or by binding to the pro-apoptotic BCL2 family members and activating their pro-apoptotic functions (10). The polymorphism switched BIM splicing from exon 4 to exon 3 which caused the BIM lacking the crucial BH3 domain (19). That leads to the lower responses to TKI than do individuals without the polymorphism. This may be the cause why BIM deletion polymorphism was associated with poor clinical outcome in EGFR-mutated NSCLC patients with TKI targeted therapy (20).

However, because the difficulty of follow-up, only about two studies offered the overall survival (OS) of patients, we cannot evaluate the influence of BIM deletion polymorphism on the EGFR-mutated NSCLC patients received EGFR-TKI. And eligible studies were a few and were only searched on the databases of the Web of Knowledge and the PubMed. Then the sample was not big enough.

In summary, BIM deletion polymorphism was associated with poor RR, DCR, PFS in EGFR-mutated NSCLC patients received EGFR-TKI. Which indicated it might be a genetic cause of intrinsic resistance to TKI therapy in EGFR-mutated NSCLC and it could be emerged as an independent predictive biomarker to identify patients who would benefit from TKI targeted therapy in EGFR-mutated NSCLC.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References
