Concomitant genetic alterations having greater impact on the clinical benefit of EGFR-TKIs in EGFR-mutant advanced NSCLC than BIM deletion polymorphism

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Abstract

Background: In previous studies, the predictive role of BIM deletion polymorphism with respect to responses to epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) has been controversial. The potential reasons for these inconsistent findings were unknown.

Methods: Data from CTONG0901 clinical trial and medical records of Guangdong Lung Cancer Institute (GLCI) were retrospectively pooled. A total of 194 and 141 EGFR-mutant non-small cell lung cancer (NSCLC) patients treated with first- and second-generation EGFR-TKIs were examined in the CTONG0901 and GLCI cohorts, respectively. Sixty-eight patients were treated with third-generation EGFR-TKIs in the GLCI cohort. The BIM gene status was examined by next-generation sequencing.

Results: The frequency of BIM deletion polymorphism was 11.3% and 17.0% in CTONG0901 and GLCI cohorts, respectively. For first- and second-generation EGFR-TKIs in CTONG0901 cohort, objective response (ORR) was 54.5% in BIM deletion group versus 56.4% in wild-type BIM group (P = .87); disease control rate (DCR) was 90.9% versus 88.4% (P = 1.00); progression-free survival (PFS) was 10.5 versus 11.2 months (P = .59); and overall survival (OS) was 20.5 versus 20.5 months (P = .73). In GLCI cohort, ORR was 54.2% versus 60.7% (P = .55); DCR was 91.7%.

Abbreviations: CML, chronic myeloid leukemia; EGFR-TKIs, epidermal growth factor receptor tyrosine kinase inhibitors; NGS, next-generation sequencing; GLCI, Guangdong Lung Cancer Institute; NSCLC, nonsmall cell lung cancer; PFS, progression-free survival; OS, overall survival; ORR, objective response rate; HR, hazard ratio; CI, confidence interval.

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versus 96.6% (P = .27); PFS was 10.1 versus 11.6 months (P = .63); and OS was 58.5 versus 45.0 months (P = .93). For third-generation EGFR-TKIs, ORR was 18.2% versus 63.2% (P = .02); DCR was 81.8% versus 96.5%, (P = .12); PFS was 5.8 versus 9.0 months (P = .13); and OS was 30.0 versus 24.8 months (P = .85). Cox regression analysis showed that concomitant genetic alterations could adversely affect the response to EGFR-TKIs, but not BIM deletion.

Conclusions: The presence of BIM deletion showed no relation to an impaired response to first-, second-, and third-generation EGFR-TKIs in NSCLC patients. The factors influencing the response of EGFR-TKIs were concomitant genetic alterations, but not BIM deletion.

KEYWORDS
BIM deletion polymorphism, concomitant genetic alterations, EGFR-TKIs, next-generation sequencing, NSCLC

1 | BACKGROUND

Previous reports have indicated that the incidence of epidermal growth factor receptor (EGFR) mutations is high in Asian populations, reaching 30% in non-small cell lung cancer (NSCLC) patients and 50% in those with adenocarcinoma.1 Patients with EGFR mutations can be treated with first-, second-, and third-generation epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs), in a first-line setting and beyond.2-6 BIM is a pro-apoptotic member of the B-cell lymphoma-2 family and plays a role in regulating apoptosis during tumor formation.7 Activated BIM exerts a pro-apoptotic action through various pathways by translocation to the mitochondrial membrane.8 BIM contains only one BH3 domain, which is essential for the pro-apoptotic activity of each BIM subtype.9 EGFR-TKIs upregulate BIM expression to induce apoptosis of lung cancer cells with EGFR mutations.10,11 Therefore, decreased BIM expression in malignant tumor inhibits tumor cell apoptosis and promotes tumor development. BIM deletion polymorphisms are common in Asian populations, with an incidence of 12-16% in lung cancer patients with EGFR mutations.12,13 Previous studies have shown that patients with EGFR mutations and BIM deletion polymorphisms are less responsive to EGFR-TKI therapy.14-16 In contrast, other studies showed that BIM deletion polymorphism had no effect on the progression-free survival (PFS) or overall survival (OS) of patients treated with EGFR-TKI therapy.14,16

The role of BIM in the induction of apoptosis of lung cancer cells, and its involvement in the primary resistance to EGFR-TKIs of lung cancer patients, has attracted attention. The available data are inconsistent regarding the predictive role of BIM deletion polymorphisms. With the advent of next-generation sequencing (NGS), concomitant genetic alterations are increasingly detected. Comprehensive genetic analysis is needed to understand the inconsistent outcomes and to identify which genetic variants have an impact on the responsiveness to EGFR-TKIs. Here, we used NGS to examine the predictive and prognostic roles of BIM deletion polymorphisms with respect to the response to first-, second-, and third-generation EGFR-TKIs in NSCLC patients from two independent cohorts.

2 | METHODS

2.1 | Patients

A total of 256 EGFR-mutant patients diagnosed with advanced-stage NSCLC were enrolled in the CTONG0901 clinical trial. The first-generation EGFR-TKIs, erlotinib or gefitinib, were given to patients as any-line treatment. Of the patients, 194 had sufficient tumor tissue at baseline for analysis by NGS using a panel of 168 genes; 22 of these patients had BIM deletion polymorphism and 172 had wild-type BIM. In

From January 2016 to July 2018, the clinical data of 141 NSCLC patients with EGFR mutations from Guangdong Lung Cancer Institute (GLCI) were retrospectively pooled. Patients were treated with first- or second-generation EGFR-TKIs as any-line treatment. The EGFR mutation status was identified by an amplification refractory mutation system or NGS. BIM deletion polymorphism represents a germline mutation, so the status of BIM was assessed by NGS at least once during the treatment process. Twenty-four patients had BIM deletion polymorphism and 117 had wild-type BIM. In
later lines of treatment, 68 patients were treated with third-generation EGFR-TKIs (11 patients in BIM deletion group and 57 in wild-type BIM group).

2.2 | NGS at baseline

A total of 194 patients in the CTONG0901 cohort (22 patients: BIM deletion; 172 patients: wild-type BIM) and 29 in the GLCI cohort (seven patients: BIM deletion; 22 patients: wild-type BIM) had NGS results at the baseline of first- and second-generation EGFR-TKIs. Thus, 223 patients were included in the final analysis of concomitant mutations and survival (29 patients: BIM deletion; 194 patients: wild-type BIM). Fresh frozen or formalin-fixed paraffin-embedded tissues from 217 patients, and peripheral plasma or cerebrospinal fluid specimens from six patients, were used for NGS testing. A total of 214 samples were analyzed with a panel of 168 genes; nine samples were analyzed with panels of 295 or 520 genes. The NGS results of 168 overlapping genes were included in the final analysis.

2.3 | Analysis

The clinical and pathological characteristics of patients with and without BIM deletion polymorphism were analyzed with SPSS version 22.0 and GraphPad Prism version 7.00. The chi-square test was used to analyze categorical data. PFS was measured from the date of EGFR-TKI treatment to the date of disease progression or last follow-up. OS was measured from the date of EGFR-TKI treatment to the date of death or last follow-up, with a cutoff date of June 2019. Kaplan-Meier survival curves were generated to estimate PFS and OS in the BIM deletion and wild-type BIM groups. Univariate analysis and multivariate Cox regression analysis were performed to determine whether the alterations in genetic background had an impact on PFS or OS in patients treated with EGFR-TKIs, in addition to BIM deletion polymorphism. The predictive and prognostic factors investigated included 167 genetic alterations, BIM deletion, PFS, and OS.

3 | RESULTS

3.1 | Clinical and pathological characteristics of BIM deletion polymorphism

The incidence rates of BIM deletion polymorphism in EGFR-mutant patients with advanced-stage NSCLC were 11.3% (22/194) and 17.0% (24/141) in the CTONG0901 and GLCI cohorts, respectively. Homozygous BIM deletion only occurred in 4.3% of patients (2/46).

The distribution of clinical and pathological characteristics in patients with and without BIM deletion in the CTONG0901 and GLCI cohorts is summarized in Table 1. There were no significant differences in age, sex, smoking history, Eastern Cooperative Oncology Group performance status score, pathology, or clinical stage between the BIM deletion and wild-type BIM groups.

3.2 | Clinical efficacy of EGFR-TKIs and BIM deletion polymorphism

The proportions of partial response, stable disease, and progressive disease were comparable between the BIM deletion and wild-type BIM groups (Figure 1A). The objective response rate (ORR) was 54.5% versus 56.4% in patients with and without BIM deletion in the CTONG0901 cohort, respectively (P = .87), and 54.2% versus 60.7% in the GLCI cohort, respectively (P = .55). The disease control rate (DCR) was 90.9% versus 88.4% in patients with and without BIM deletion in the CTONG0901 cohort, respectively (P = 1.00), and 91.7% versus 96.6% in the GLCI cohort, respectively (P = .27). The median PFS and OS were not significantly different between patients with and without BIM deletion in the CTONG0901 cohort (PFS: 10.5 vs 11.2 months, respectively, P = .59; OS: 20.5 vs 20.5 months, respectively, P = .73) (Figures 2A and 2D). Similar results were obtained in the GLCI cohort (PFS: 10.1 vs 11.6 months, respectively, P = .63; OS: 58.5 vs 45.0 months, respectively, P = .93) (Figures 2B and 2E). Subgroup analysis was performed in patients with EGFR 19 deletions and 21L858R mutations. The median PFS and OS also showed no association with BIM status in either cohort (Figures S1 and S2). BIM deletion polymorphism was not associated with a poorer curative effect of EGFR-TKIs in two independent cohorts.

Similar analyses were performed in patients treated with the third-generation EGFR-TKIs, osimertinib and avitinib. The ORR was lower in the BIM deletion group than in the wild-type BIM group (18.2% vs 63.2%, respectively, P = .02). The DCR was 81.8% in the BIM deletion group and 96.5% in the wild-type BIM group (P = .12) (Figure 1B). The median PFS and OS were comparable between the two groups (PFS: 5.8 vs 9.0 months, respectively, P = .13; OS: 30.0 vs 24.8 months, respectively, P = .85) (Figures 2C and 2F).

3.3 | Relations of concomitant genetic alterations to EGFR-TKI responsiveness

We examined the potential reasons for the inconsistent outcomes in previous studies regarding the relation between BIM deletion and the response to EGFR-TKIs. Along with the results of NGS, all genetic alterations and BIM deletion...
|                      | CTONG0901 cohort |                      | GLCI cohort |                      | P-value |
|----------------------|------------------|----------------------|-------------|----------------------|---------|
|                      | BIM deletion     | Wild-type BIM        |             |                      |         |
|                      | (n = 22)         | (n = 172)            |             |                      |         |
| Age in years, mean ± SD | 59.1 ± 11.2      | 58.7 ± 11.2          |             |                      |         |
| Age in years, n (%)   |                  |                      |             |                      |         |
| < 65                 | 17 (77%)         | 121 (70%)            |             |                      | .50     |
| ≥ 65                 | 5 (23%)          | 51 (30%)             |             |                      |         |
| Sex, n (%)           |                  |                      |             |                      |         |
| Male                 | 12 (55%)         | 80 (47%)             |             |                      | .48     |
| Female               | 10 (45%)         | 92 (53%)             |             |                      |         |
| Smoking histology, n (%) |              |                      |             |                      |         |
| Never                | 17 (77%)         | 136 (79%)            |             |                      | .85     |
| Former/Current       | 5 (23%)          | 36 (21%)             |             |                      |         |
| ECOG PS, n (%)       |                  |                      |             |                      |         |
| 0-1                  | 22 (100%)        | 169 (98%)            |             |                      | 1.00    |
| ≥ 2                  | 0 (0%)           | 3 (2%)               |             |                      |         |
| Pathology, n (%)     |                  |                      |             |                      |         |
| Adenocarcinoma       | 22 (100%)        | 164 (95%)            |             |                      | .60     |
| Squamous carcinoma   | 0 (0%)           | 3 (2%)               |             |                      |         |
| Others               | 0 (0%)           | 5 (3%)               |             |                      |         |
| Stage, n (%)         |                  |                      |             |                      |         |
| IIIb                 | 0 (0%)           | 5 (3%)               |             |                      | 1.00    |
| IV                   | 22 (100%)        | 167 (97%)            |             |                      |         |
| EGF RTKIs, n (%)     |                  |                      |             |                      |         |
| First-generation     | 22 (100%)        | 172 (100%)           |             |                      |         |
| Second-generation    | –                | –                    |             |                      |         |
| Line of first- and second-generation EGFR-TKIs, n (%) | | | | | |
| First line           | 19 (86%)         | 113 (66%)            |             |                      | 0.09    |
| Second line and beyond | 3 (14%)       | 59 (34%)             |             |                      |         |
| Line of third-generation EGFR-TKIs, n (%) | | | | | |
| First line           | –                | –                    |             |                      | 1 (9%)  |
| Second line          | –                | –                    |             |                      | 7 (12%) |
| Third line and beyond | –                | –                    |             |                      | 3 (27%) |

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; EGFR-TKIs, epidermal growth factor receptor tyrosine kinase inhibitors.

polymorphisms were input into univariate and multivariate analyses to identify which concomitant genetic variations were associated with impaired or enhanced curative effects of EGFR-TKIs. The heat map showed the EGFR mutation subtypes, BIM status, and concomitant genetic variations detected in at least three patients (Figure S3). The frequency of concomitant TP53 mutation was the highest, which was 58.6% (17/29) in BIM deletion group and 68.0% (132/194) in wild-type BIM group. Further, we screened the genes identified by NGS to determine which had an influence on the PFS and OS of patients treated with EGFR-TKIs. Cox multivariate regression analysis showed that four genetic
alterations were associated with poorer PFS—TP53 mutation (hazard ratio [HR] = 1.5; 95% confidence interval [CI], 1.10-2.00; \( P = .01 \)), NTRK1 mutation and amplification (HR = 4.7; 95% CI, 1.64-13.40; \( P = .04 \)), RB1 mutation (HR = 1.7; 95% CI, 1.06-2.8; \( P = .03 \)), and PIK3CA mutation (HR = 1.7; 95% CI, 0.99-3.00 \( P = .05 \)) were the strongest independent predictors of shorter PFS in patients treated with EGFR-TKIs (Figure 3A). In addition, two genetic alterations were shown to have an impact on OS in patients treated with EGFR-TKIs—TP53 mutation was the strongest independent predictor of a shorter OS (HR = 1.50; 95% CI, 1.10-2.06; \( P = .01 \)). KEAP1 mutation and deletion was the strongest independent predictor of a longer OS (HR = 0.12; 95% CI, 0.02-0.88; \( P = .04 \)) (Figure 3B). Thus, neither analysis showed an effect of BIM deletion polymorphism on PFS and OS in NSCLC patients treated with EGFR-TKIs.

4 | DISCUSSION

In 2012, Ng reported that BIM deletion polymorphism mediated primary resistance to TKIs in cancers including chronic myeloid leukemia (CML) and EGFR-mutant NSCLC; this was confirmed by in vitro cell culture experiments and clinical data.\(^{14}\) Subsequently, two studies from Japan indicated that BIM deletion was associated with a reduced benefit of first- and third-generations EGFR-TKIs, based on the results of in vitro and in vivo experiments.\(^{18,19}\) However, in 2014, this finding was challenged by Chinese researchers with the conclusion that the BIM deletion polymorphism cannot account for intrinsic TKI resistance of Chinese individuals with CML.\(^{20}\) Subsequent studies with clinical data in EGFR mutant NSCLC were inconsistent regarding the predictive role of BIM deletion polymorphism with respect to the responsiveness to first-generation EGFR-TKIs. Two studies from Korea\(^{13,17}\) and one from China\(^{21}\) showed that BIM deletion polymorphism was not an independent predictor of a poor response to EGFR-TKIs in EGFR-mutant NSCLC patients, whereas other studies\(^{15,16,22}\) and studies detecting BIM mRNA expression\(^{23,24}\) reported the opposite results. However, BIM deletion polymorphism was not a prognostic biomarker for OS in most studies. In the present study, BIM deletion polymorphism had no influence on the PFS or OS of patients treated with first- and second-generation EGFR-TKIs in two independent cohorts. In general, almost half of the clinical studies did not replicate the results of cell line experiments regarding the effects of BIM deletion on the response to EGFR-TKIs. It is inevitable for the occurrence of drug resistance after patients treated with first- or second-generation of EGFR-TKIs for 9-12 months.\(^{25,26}\) A total of 50% NSCLC patients carried EGFR T790M mutation and third-generation EGFR-TKIs would be the optimal choice for the next-step treatment.\(^{6}\) To date, with the exception of one case report,\(^{27}\) there have been no reports based on clinical data regarding the impact of BIM status on the response to third-generation EGFR-TKIs. In our study, although patients with BIM deletion...
FIGURE 2 Survival analysis of the progression-free survival (PFS) and overall survival (OS) of patients with and without BIM deletion polymorphism treated with first-generation EGFR-TKIs in the CTONG0901 cohort (A and D) and treated with first- and second-generation EGFR-TKIs in the GLCI cohort (B and E). Survival analysis of PFS and OS of patients with and without BIM deletion polymorphism treated with third-generation EGFR-TKIs in GLCI cohort (C and F).

**Abbreviations:** BIM del, BIM deletion; BIM wt, wild-type BIM.

...tended to have a poor response to osimertinib or avitinib, the DCR, PFS, and OS were comparable to those of patients without BIM deletion. The small sample size of patients treated with third-generation EGFR-TKIs likely leads to selection bias, which could explain the lower ORR in the BIM deletion groups.

This study verified our hypothesis that, in addition to BIM deletion polymorphism, the genetic background could also have an impact on the responsiveness to EGFR-TKIs. The presence of TP53, RB1, and PIK3CA mutations reduced the response to TKIs. Here, we attempted to give an explanation of the inconsistent evidence regarding the role of BIM deletion in the responsiveness to EGFR-TKIs and identify why some clinical reports could not replicate the results of in vitro and in vivo experiments. First, with the advent of NGS, the genetic background with hundred genes could be profiled and the results should be taken into account when analyzing the influential factors to clinical benefit of EGFR-TKIs. The co-mutation profile of NSCLC patients has been landscaped in previous study.28 It was reported that concomitant mutation was associated with reduced response and poor survival of EGFR-TKIs.29 Our study found that patients with TP53 or RB1 mutation tended to show an impaired response to EGFR-TKIs. However, the detection method of BIM status in published studies could not profile the genetic background.13,16,17 Second, the incidence of BIM deletion in EGFR mutant patients with NSCLC was around 15% in these previous reports15,21 and in our study. The small sample sizes led to a large degree of heterogeneity in the BIM deletion group. When more patients combined with TP53 or RB1 mutation included in this group, the outcome would be that BIM deletion had a more deleterious response to EGFR-TKIs than wild-type BIM. Third, it is apparent that some studies with clinical data could not replicate the results of in vitro and in vivo experiments in other research. As we know, the cell lines were pure, carrying only one or two mutations. However, the situation in clinical practice is usually more complex, where the presence of certain confounding factors is inevitable.

This study had some limitations. First, although our study had the largest sample size of EGFR-mutant patients with known BIM status reported to date, only 68 patients were included in the survival analysis of treatment with third-generation of EGFR-TKIs. Second, baseline NGS results...
The result of cox regression analysis to identify which concomitant genetic variations were associated with impaired or enhanced curative effects of EGFR-TKIs. BIM deletion and concomitant genetic variations detected in at least three patients were presented. A, Genetic factors influencing the PFS of patients treated with EGFR-TKIs. B, Genetic factors influencing the OS of patients treated with EGFR-TKIs. The outside circle represents the genes included in Cox regression analysis. The inside circle represents the results of the multivariate analysis; statistically significant $P$-values are provided. The different colors and sizes of circles represent the hazard ratio and sample size of patients with corresponding genetic alterations, respectively.

were available for only 24 patients with BIM deletion, which may have been an insufficient sample size to examine the role of BIM status in Cox regression analysis. Third, the mechanism underlying the lack of effect of BIM deletion polymorphism on responsiveness to EGFR-TKIs remains unclear.

5 | CONCLUSION

Overall 11.3% and 17.0% EGFR-mutant patients with advanced-stage NSCLC in the CTONG0901 and GLCI cohorts had BIM deletion polymorphism, respectively, which had no relationship with any clinical or pathological factors. The presence of BIM deletion was not associated with impaired survival in patients treated with first-, second-, and third-generation EGFR-TKIs. Concomitant genetic alterations, but not BIM deletion polymorphism, had an influence on the clinical benefit of EGFR-TKIs in patients with advanced NSCLC.

AUTHOR CONTRIBUTIONS

Yi-Long Wu was associated with conception and design of the study. Si-Yang Liu, Jia-Ying Zhou, Hao Sun, Yi-Chen Zhang, Zhi-Hong Chen, Jin-Ji Yang, Qing Zhou, and Xu-Chao Zhang acquired the clinical data. Si-Yang Liu, Wen-Feng Li, Hong-Hong Yan, Chun-Xiang Chen, and Jun-Yi Ye analyzed and interpreted the data. Si-Yang Liu and Jia-Ying Zhou drafted and revised the manuscript. All authors approved the final manuscript.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AVAILABILITY OF DATA AND MATERIALS

The data that support the findings of this study are available from Yi-Long Wu upon reasonable request.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

All patients provided written informed consent for the use of their tumor specimens. CTONG09001 clinical trial has been approved by the ethics committee of Guangdong Provincial People’s Hospital.

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SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section at the end of the article.

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