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Meta-Analysis

Association between BIM polymorphism and lung cancer outcomes: a meta-analysis

Xiao-feng Li[1], Li-xin Wu[1], Hua-fei Chen[1], You-cai Zhu[1], Wen-xian Wang[2], Chun-wei Xu[3], Xue-ping Lin[4*], Dong-fang Xie[5], Kai-qi Du[1]

[1] Department of Thoracic Disease Center, Zhejiang Rongjun Hospital, Jiaxing Zhejiang 314000, People's Republic of China
[2] Department of Chemotherapy, Zhejiang Cancer Hospital, Hangzhou Zhejiang 310022, People's Republic of China
[3] Department of Pathology, Fujian Cancer Hospital, Fujian Medical University Cancer Hospital, Fuzhou Fujian 350014, People's Republic of China
[4] Department of Pathology, Jiaxing University College of Medicine, Jiaxing Zhejiang 314000, People's Republic of China
[5] Department of Pathology, Zhejiang Rongjun Hospital, Jiaxing Zhejiang 314000, People's Republic of China

Correspondence to: li_xueping@sina.cn

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Abstract: Accumulating evidences have indicated that BIM expression largely decides the development of lung cancer and outcome of EGFR-mutant lung cancers after TKI treatments. BIM polymorphism is a 2,903-bp deletion in the second exon. To clarify the relationship between this BIM polymorphism and clinical outcomes of lung cancers, we conducted this meta-analysis and observed the survival and responses to TKIs. Sixteen cohort studies, covering 4393 WT and 916 BIM deletion patients were included. Overall, BIM deletion polymorphism was associated with significantly shorter progression-free survival (PFS) and slightly shorter overall survival (OS), compared to the WT group. Moreover, patients with BIM deletion polymorphism showed significantly inferior response to EGFR TKIs. In conclusion, our analysis confirmed that lung cancer patients harboring the BIM deletion have inferior survival and TKI responses. Examination of the novel biomarker BIM deletion in lung cancer patients, especially for the EGFR mutant cohort, could provide some prognostic utility.

Key words: BIM polymorphism; Bcl-2-like 11; EGFR mutation; Lung cancer; Tyrosine kinase inhibitor.

Introduction

Lung cancer is the leading cause of cancer-related death in China and even over the world (1). There have been some recognized genes, like Kras, EGFR, etc., reported to influence the development of lung cancers. Particularly, large amounts of lung cancer patients are due to mutated EGFR, which are generally recommended targeted therapy, for example tyrosine kinase inhibitor (TKI). Recently, Bcl-2-like 11 (BCL2L11 or BIM), a member of the Bcl-2 family, has been discovered and increasingly aroused the interest of cancer researchers. BIM plays a key role in promoting apoptosis. Therefore, it could influence the progress of lung cancers and prognosis in all probability (2). Accumulating evidences have indicated that the expression of BIM largely decides not only the development of lung cancer but also the outcome of EGFR-mutant lung cancers after TKI treatments (3-5). BIM polymorphism mainly refers to a 2,903-bp deletion in the second exon. BIM deletion usually leads to alternative splicing of BIM mRNA. BIM loss was hypothesized to attenuate the apoptosis even under the TKI condition, and theoretically those patients with BIM deletion may show a significant resistance to TKI treatment. This was confirmed by some typical references (6-8). However, controversial studies exist as well, that some researchers reported no significance of BIM polymorphism in lung cancer development (9, 10). To clarify the relationship between this BIM polymorphism and clinical outcomes of lung cancers, we conducted this meta-analysis and observed several most important indexes, like progression-free survival (PFS), responses to TKIs, and so on. BIM polymorphism has been confirmed highly associated with the clinical responses to TKIs and survival outcome of lung cancer patients.

Materials and Methods

Literature search strategy

This review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Literatures were searched using the following key words: “BIM” or “BCL-2-like 11” or “BCL2-like 11” or “BCL-2 like 11” AND “polymorphism” AND “lung cancer”. We collected data from the all full-published English papers, not any meeting or conference abstract. A thorough literature search was undertaken using the following databases: PubMed (http://www.ncbi.nlm.nih.gov), Embase (http://www.embase.com), and Science Direct (http://www.sciencedirect.com) databases. Abstracts were scrutinized, and full articles were analyzed. The literature retrieval was performed by two independent authors. And no language or date restrictions were found in literature collection.

Inclusion and Exclusion Criteria

As figure 1 shown, the inclusion criteria were as follow. (1) Type of study: studies should be clinical randomized controlled trials (RCTs); (2) Publication in the PubMed, Embase, Cochrane, and Web of Science data-

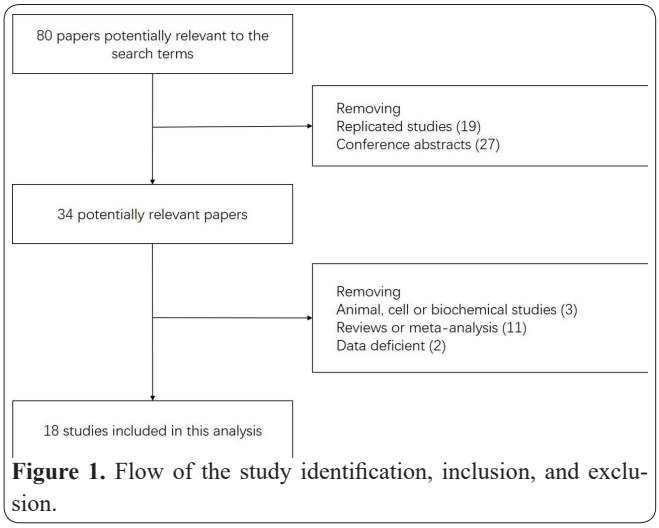

Figure 1. Flow of the study identification, inclusion, and exclusion.

bases; (3) Lung-cancer studies; (4) Clinical outcomes were stratified by BIM polymorphism status; (5) The direct results including indexes we were interested in were available.

The exclusive criteria were as follow, besides replication removing: (1) Not regarding to the BIM gene polymorphism; (2) Not clinical studies; (3) Conference abstracts, comments, reviews or meta-analysis; (4) Insufficient data: no detailed data about BIM gene subtypes, patient progression or survival, or no control group existed.

Indexes to Observe

The following indexes, as well as the mutual relationships, were observed in different groups, if documented: survival time (Medium), Recurrence-free survival (RFS), Post-recurrence survival (PRS), hazard ratio (HR) of PRS for BIM polymorphism, overall survival (OS), HR of OS for BIM polymorphism.

Statistical Analysis

All data were obtained only from the lung cancer population. The health controls were excluded if documented in studies. Data were analyzed with RevMan software (version 5.3; Cochrane Collaboration, Oxford, UK). The quality of a study was regarded as high if all aspects were assessed acceptable. Mean differences (MDs) with 95% confidence intervals (CIs) were calculated for the continuous measures. The adjusted HR was used when reported in the original papers. Forest plots were presented after analysis, in which lines represented different estimates and CIs, and boxes represented the weight given to each study. HRs in the forest plots were all represented in the log(HR) form. We also quantified the effect of heterogeneity using I2. Substantial heterogeneity across the studies was detected when I2 was > 50% or the p-value for heterogeneity was < 0.10. All the P-values were two-sided. A P value less than 0.05 was considered to be statistically significant, while the P value less than 0.1 was considered to be significant statistically in heterogeneity analysis.

Results

Search Results

For initial searches, there were 80 papers potentially relevant to the search terms (PubMed: 34, Embase: 56, Web of Science: 0, Cochrane: 0). Among them, 19 duplicate studies were removed, and 27 conference abstracts were excluded. Then, the following three types of studies were further removed: animal, cell or biochemical studies (3 papers), reviews or meta-analysis papers (11 papers), and those clinical studies found insufficient of required indexes we focused on (4 papers). Eventually, data from the remaining 16 papers were used for meta-analysis (6-24). As a whole, 4393 WT and 916 BIM deletion patients were included. The characteristics of our selected studies were presented in table 1.

Patients with BIM deletion have shorter PFS

Using these included studies, we analyzed the association between the BIM deletion polymorphism and clinical outcomes. First, we compared differences in PFS. Three studies were used for continuous analysis,

Table 1. Characteristic of the included studies.

Study	WT patients			BIM-deletion patients		
	Number	Average Age	Gender (M/F)	Number	Average Age	Gender (M/F)
Atsumi 2015	350	67.9	198/152	61	66.5	38/23
Cardona 2016	75	60.8	22/53	14	52.6	5/9
Cho 2015	343	63.4 ± 11.0	226/117	63	64.5 ± 9.5	41/22
Isobe 2014	57	65.4±14.1	15/42	13	63.8±6.7	4/9
Isobe 2016	29	-	-	4	-	-
Lee 2013	172	-	-	21	-	-
Lee 2014	171	61.7	65/106	33	66.7	15/18
Lee 2015	173	59±10	59/114	32	59±10	7/25
NG 2012	200	-	-	200	-	-
Qian 2017	71	-	26/45	14	-	4/10
Xia 2016	2005	-	1324/681	338	-	234/104
Zhang 2017	60	52 (23-81)	31/29	9	51 (39-68)	2/7
Zhao 2014	307	59 (32-81)	153/154	45	59 (39-75)	20/25
Zheng 2013	102	-	-	21	-	-
Zhong 2014	245	58.33±11.73	105/140	45	59.98±11.08	23/22
Zhou 2014	33	-	-	3	-	-

which were demonstrated as mean and standard errors. The PFS time (months) in BIM-deficient patients were shorter than the WT (Fig. 2A). Howell, the amount of studies was limited and thus no statistical significance was found (Test for overall effect Z = 1.85, P = 0.06), and no significant heterogeneity was observed (Tau² = 8.34, Chi² = 4.97, P = 0.08, I² = 60%). On the other hand, seven studies have calculated the hazard ratio (HR) of BIM deletion towards PFS (Fig. 2B), and significant association was found between BIM deletion polymorphism and PFS, which highly suggested BIM deletion was a hazard predictor for short PFS (Test for overall effect: Z = 5.72, P < 0.00001). Nevertheless, significant heterogeneity existed (Heterogeneity: Chi² = 25.31, P = 0.0003, I² = 76%), especially considering a study from Lee in 2015 claimed that BIM deletion could mean longer PFS.

Patients with BIM deletion have shorter OS

Next, we compared OS between two groups. Different from PFS, fewer studies have documented the OS indexes. Two studies demonstrated the hazard ratio of BIM deletion regarding to OS (Fig. 3A). Similar to PFS, OS was also shorter in BIM deletion patients compared to WT (Test for overall effect: Z = 3.08, P = 0.002), without significant heterogeneity (Heterogeneity: Chi² = 1.97, P = 0.16, I² = 49%). Only one study showed the months of OS (Fig. 3B), and the OS of patients with BIM deletion was slightly shorter (not significantly different) than the WT group (Test for overall effect: Z = 0.53, P = 0.59).

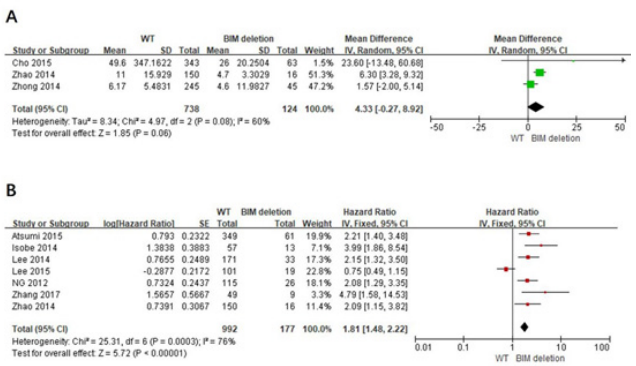

Figure 2. Cumulative meta-analysis of the progression-free survival (PFS) between the BIM deletion polymorphism and the WT patients. (A) The PFS time (months) in BIM-deficient patients was shorter than the WT, presented as forest plots. (B) the hazard ratio (HR) of BIM deletion towards PFS (presented as forest plots).

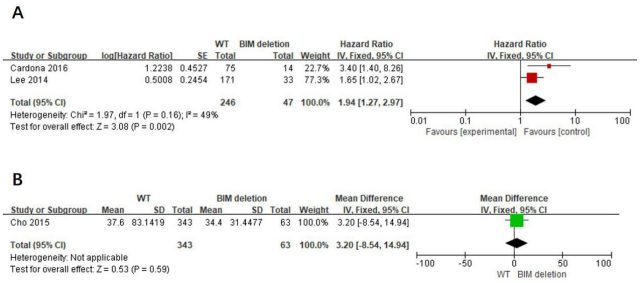

Figure 3. The overall survival (OS) indexes of two groups. Different from PFS, fewer studies have documented the OS indexes. (A) Two studies demonstrated the hazard ratio of BIM deletion regarding to OS, which was also shorter in BIM deletion patients compared to WT. (B) Only one study showed the months of OS.

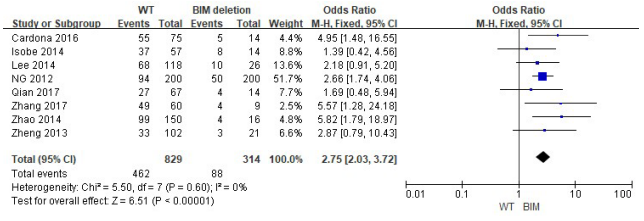

Figure 4. BIM deletion patients showed significantly poorer responses to EGFR-TKIs.

BIM deletion implied poor TKI responses

Eight studies were aggregated for odds ratio analysis of TKI response, which included 462 WT and 88 BIM-deficient patients. As figure 4 shown, all these studies consistently concluded that BIM deletion means significantly poorer TKI response (complete or partial response, Test for overall effect: Z = 6.51, P < 0.00001), and no significant heterogeneity was observed (Heterogeneity: Chi² = 5.50, P = 0.60, I² = 0%). This result is consistent with the above conclusion that BIM is associated with significant poor survival (PFS or OS).

Other factors associated with BIM deletion

In consistent, some independent studies included in this analysis also highlight a tumor-promoting role of BIM deletion polymorphism. For example, Isobe et al reported that BIM-γ RNA expression was significantly higher in patients with BIM deletion polymorphism, and patients with BIM-γ had significantly shorter progression-free survival than those without BIM-γ (21).

Parallelly, there have been some studies suggesting that BIM deletion has no relationship with survival (OS or PFS). Lee had reported in 2013 that patients with BIM deletion polymorphisms and wild-type alleles exhibited no difference in PFS (6). Xia et al also claimed that BIM deletion polymorphism was no related with age, sex, and smoking or EGFR mutation (16). Zhou et al showed that neither BIM polymorphic deletion nor EGFR mutation had strong correlation with the efficacy of sorafenib (a useful TKI) (11). However, Xia and Zhou did not provide any detailed data and thus their studies were not added in the forest plots for analysis.

Finally, we found no publication bias for conclusions funnel plot analysis, for significant symmetrical appearance were demonstrated for PFS measure and TKI responses (not shown).

Discussion

In this work, we conducted a meta-analysis using 16 studies and confirmed that BIM deletion predicts the inferior outcome, especially in the progression-free survival and response to TKIs. BIM deletion polymorphism could independently predict shorter survival of lung cancer patients. Statistically, we found no strong evidences deciding that BIM deletion significantly reduces OS in comparison with WT patients. EGFR mutation underlies the mechanism of a large proportion of lung cancers, majorly in non–small-cell lung carcinoma (NSCLC). We didn't intentionally screen for EGFR mutant types or NSCLCs, but almost all the studies included observed NSCLC patients with EGFR mutation, and most of them had been treated by EGFR-TKIs.

Different biomarkers have been implied associated with the final outcome of TKIs treatment or lung cancer progression. Here, BIM polymorphism demonstrated an effectiveness and consistency in prognosis prediction. These conclusion is consistent with some published studies. Huang el al summarized a mechanism of EGFR-TKIs that they lead to cell death through BIM-mediated apoptosis (25). Similar studies conducted by Li's group, Wang's group and Song's group (all in 2015) reported that BIM deletion polymorphism was predictive of shorter PFS in NSCLC patients and intrinsic resistance to EGFR-TKI treatments (26-28). Thereafter, Lim et al also confirmed BIM deletion is a significant predictor of shorter PFS and OS on EGFR-TKIs in 2017 (29), which was further proved by Wang's group (30).

However, there are some reviews or meta analysis not fully supporting our conclusion. Cai et al analyzed 6 studies and found only marginal improvements but not statistical significance in objective response rates between BIM deletion and the WT groups (31). But their study still agreed that, for patients, WT NSCLC patients have longer PFS than those with BIM polymorphism after EGFRTKIs treatment. Admittedly, these reviews are limited in sample amounts and detailed data in some indexes, and further studies are warranted to complete the information. On the other aspect, we demonstrated the BIM deletion implied poor survival, which suggests the BIM deletion is positively related with lung cancer development. However, one study probed the relationship between BIM deletion and lung cancer susceptibility and EGFR mutation. They found the BIM deletion polymorphism was neither associated with lung cancer susceptibility nor EGFR mutation (10). In combination of our observation, the contribution of BIM deletion to lung cancer progression may mainly depend on a loss of TKI response in the EGFR mutant population. Matsuo et al also pointed out in their review that BIM polymorphism does not appear to be associated with a higher risk to develop lung cancer, while its utility to determine treatment options is signifiant (10).

In conclusion, our analysis confirmed that lung cancer patients harboring the BIM deletion have inferior survival and TKI responses. Examination of the novel biomarker BIM deletion in lung cancer patients, especially for the EGFR mutant cohort, could provide some prognostic utility.

Acknowledgments

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Conflicts of Interest

We declare no competing interests exist.

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