Original

Alectinib Versus Crizotinib for Previously Untreated Alk-positive Advanced Non-small Cell Lung Cancer : A Meta-Analysis

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Abstract : The safety and efficacy profiles of alectinib versus crizotinib for patients with previously untreated anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer still remains to be elucidated. We compared the overall efficacies of alectinib and crizotinib for previously untreated ALK-positive advanced non-small cell lung cancer through a meta-analysis of randomized controlled trials. The primary outcome was progression-free survival (PFS). Pooled estimates were calculated as hazard ratios with 95% confidence intervals. Two studies on alectinib met the inclusion criteria for this meta-analysis. The hazard ratio (95% confidence interval) of alectinib for PFS, relative to crizotinib, was 0.41 (0.28–0.60), demonstrating a superior overall efficacy of alectinib over crizotinib, in terms of PFS.

Key words : meta-analysis, alectinib, crizotinib, non-small cell lung cancer, anaplastic lymphoma kinase

Introduction

Lung cancer is the most common cause of cancer-related death worldwide. Approximately 80% of lung cancer cases comprise non-small cell lung cancer (NSCLC)[1]. The 5-year survival rate for patients with lung cancer is only approximately 15%. Furthermore, patients with advanced NSCLC are generally considered to have a poor prognosis, with a median survival period of 8–10 months[1,2].

Anaplastic lymphoma kinase (ALK) is a receptor tyrosine kinase belonging to the insulin receptor superfamily[3,4]. Various ALK gene alterations have been identified across a range of tumor types, including point mutations, deletions, and rearrangements. Numerous ALK fusions occur during cancer[4]. In particular, echinoderm microtubule-associated protein-like 4 (EML4)-ALK, a fusion gene, occurs predominantly in NSCLC. In a study conducted in 2007, EML4-ALK was identified in patients with NSCLC and was defined as a new molecular subset highly sensitive to ALK inhibition[3].

The first ALK inhibitor, crizotinib, was approved by the US Food and Drug Administration as a therapeutic option for NSCLC in 2011 and was first used in Japan in 2012[5]. Since then,

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ALK has been defined as a novel molecular target for NSCLC treatment. However, most patients experience disease progression less than a year after starting treatment with crizotinib, partially because crizotinib shows diminished therapeutic efficacy against various ALK point mutations, as well as metastasis to the central nervous system[5].

Several second-generation ALK inhibitors are currently available as treatment options for NSCLC, and third-generation ALK inhibitors are under clinical investigation or at the preclinical research stage. Alectinib, a second-generation ALK inhibitor, has recently been approved in Japan for crizotinib-refractory ALK-rearranged NSCLC or advanced NSCLC[6]. A previous clinical study reported that alectinib is effective in most crizotinib-resistant ALK mutations, with a tolerable safety profile[6]. Recently, large-scale randomized controlled trials（RCTs）of alectinib versus crizotinib treatment efficacy have been completed and the results have revealed that alectinib is superior to crizotinib, in terms of progression-free survival（PFS）and safety profile[7,8]. On this basis, alectinib is now expected to be the cornerstone of the first-line treatment for patients with previously untreated ALK-positive advanced NSCLC[9].

However, a meta-analysis to confirm the overall efficacy and safety of alectinib compared with crizotinib is yet to be conducted. Therefore, relevant statistical data are needed to verify the overall efficacy of alectinib compared to crizotinib in patients with previously untreated ALK-positive advanced NSCLC. In the present study, we aimed to statistically assess and compare the overall efficacy profiles of alectinib and crizotinib via a meta-analysis of RCTs, and provide an explanation for the overall effect of alectinib versus crizotinib.

Materials and methods

Literature search

We searched the MEDLINE（PubMed）, Scopus, and Cochrane library databases for studies published up to July 2017 using the following terms："lung cancer," "alectinib," and "crizotinib". No restriction was imposed on the search language. Additional relevant articles were also searched in the reference lists of the retrieved articles. The electronic databases were independently searched by two investigators（RM and KA）. In the case of any discrepancies arising between the two investigators, a third investigator（TO）conducted additional evaluations or our research team resolved the discrepancy through discussions.

Inclusion and exclusion criteria

Studies were considered eligible if they met the following criteria：1）studies should involve RCTs on the clinical efficacy of alectinib versus that of crizotinib in patients diagnosed with previously untreated ALK-positive advanced NSCLC；and 2）studies should include a PFS outcome. Observational, case-control, cohort, and non-blind clinical trials were excluded. All references were independently screened by KA and TO in accordance with the inclusion and exclusion criteria.

Data extraction

Relevant data from the eligible studies were extracted on the basis of the predefined criteria for this meta-analysis. The primary outcome was PFS.

Assessment of the risk of bias

The Cochrane-recommended methodology[10] was employed to examine each of the selected studies for potential bias arising from random sequence generation ; allocation concealment ; blinding of participants or personnel and outcome assessment ; incomplete outcome data ; selective reporting ; and other factors.

Statistical analysis

Statistical heterogeneity among the trials was assessed using the I^2 statistic[11], which measures the degree of heterogeneity in outcome measures by calculating the percentage of total variation among the included studies. I^2 values of $\geq 50\%$ indicate significant heterogeneity. The significance of heterogeneity was tested using the χ^2 statistic. Random-effects models were developed, regardless of the presence or absence of statistically significant heterogeneity.

The predefined primary and secondary outcomes of alectinib and crizotinib treatment were compared using the statistical method of inverse variance. Pooled estimates are presented as hazard ratios (HRs) with 95% confidence intervals. All analyses were performed using the RevMan software package (version 5.3, Cochrane Corporation, Oxford, UK).

Results

Study characteristics

The study selection process is shown in Fig. 1. We identified 66 manuscripts, of which 19 remained after removing duplicates. After title/abstract and full-text screening, two reports[7,8],
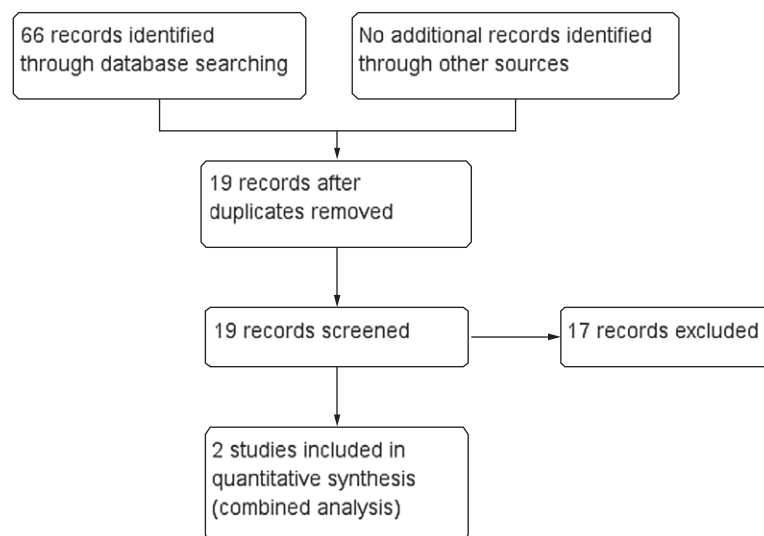

Fig. 1. Study selection process

including a total of 510 patients, were ultimately included in the present meta-analysis.

The study characteristics are listed in Table 1. The sample size ranged from 207 to 303 patients. The mean age ranged from 53.8 to 61.0 years. One study included only Japanese patients, whereas the other study included both Asian and non-Asian patients.

Bias assessment

On evaluating the selected studies for the risk of potential bias arising from random sequence generation, allocation concealment, blinding of participants or personnel and outcome assessment, incomplete outcome data, selective reporting, and other factors, we found that all the studies exhibited a low risk of bias for all factors. Figures 2A and 2B present the assessments performed by the authors of the present study for the risk of bias. No studies were excluded from this meta-analysis owing to poor quality or a difference in baseline characteristics.

Primary outcome

Two studies had comparatively assessed the difference in PFS between alectinib and crizotinib treatment. There was no significant inter-study heterogeneity among the studies that comparatively assessed overall survival after treatment with alectinib or crizotinib ($I^2 = 30\%$; $P = 0.23$). A combined analysis of these comparisons was performed using a random-effects model. The results revealed that PFS was significantly longer for alectinib than for crizotinib, with an HR (95% confidence interval) of alectinib relative to crizotinib of 0.41 (0.28–0.60).

Discussion

In this meta-analysis, we compared the efficacy of alectinib treatment with that of conventional crizotinib treatment in patients with previously untreated ALK-positive advanced NSCLC. As expected, the results of the combined analysis revealed that patients who received alectinib exhibited a significantly greater PFS than those who received crizotinib.

Previous phase-3 studies compared the efficacies of alectinib and crizotinib in patients with previously untreated ALK-positive advanced NSCLC[7,8]. These studies demonstrated the

Table 1. Characteristics of the studies included in the present meta-analysis

Study	Year of publication	Type of study	No. of patients (M / F)	Criteria	Drugs and dosages	Primary endpoint
Hida *et al*[7]	2017	RCT	207 (82 / 125)	Previously untreated ALK-positive advanced NSCLC	300 mg alectinib taken twice daily or 250 mg crizotinib taken twice daily	PFS
Peters *et al*[8]	2017	RCT	303 (132 / 171)	Previously untreated ALK-positive advanced NSCLC	600 mg alectinib taken twice daily or 250 mg crizotinib taken twice daily	PFS

RCT, randomized controlled trial; ALK, anaplastic lymphoma kinase; NSCLC, non-small cell lung cancer; PFS, progression-free survival

Fig. 2. Summary of bias assessment
A：The risk of bias graph shows items determined by the authors as having a
risk of bias（presented as percentages）in each included study.
B：Summary of risk of bias shows items determined by the authors as
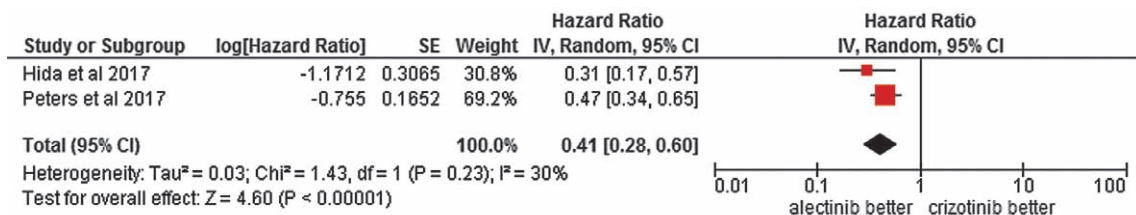presenting a risk of bias in each included study.

Fig. 3. Forest plot of progression-free survival. Comparisons between alectinib and crizotinib are shown. CI,
confidence interval ; IV, inverse variance ; SE, standard error.

superiority of alectinib over crizotinib, in terms of PFS, and also reported a better safety profile
associated with alectinib treatment compared to crizotinib treatment.

The results of the present combined analysis revealed that the efficacy profiles for alectinib
and crizotinib were similar to those reported in the previous phase-3 studies. The present results
support the hypothesis that alectinib is more effective against previously untreated ALK-positive

advanced NSCLC than crizotinib, with regard to PFS.

To our knowledge, the present study is the first meta-analysis assessing the overall efficacy and safety of alectinib versus crizotinib in previously untreated ALK-positive advanced NSCLC. This combined meta-analysis of studies was essential to confirm the results of the previous phase-3 studies. We have previously demonstrated that alectinib is more effective and better tolerated than crizotinib, even in the general population. This combined analysis was meaningful from a clinical standpoint because the results reveal the overall effect size of the hazard ratio in patients with previously untreated advanced NSCLC treated with alectinib as opposed to those treated with crizotinib.

Several limitations of the present meta-analysis should be acknowledged. First, we only considered published studies, which might have contributed toward publication bias. Second, we used a random-effects model to account for the significant heterogeneity among the included studies, and data on heterogeneity could only be partially collected. Third, the drug dosages and frequency of administration varied among the studies included in the present meta-analysis, and this may have affected the final conclusions. Fourth, the patients' characteristics varied among the studies included in the present meta-analysis. Finally, the sample size in the present study was small : only 2 RCTs were analyzed. A meta-analysis of 2 studies is not uncommon, as seen in studies on orphan diseases. Nevertheless, issues addressed by these meta-analyses might be considered unresolved in the presence of heterogeneity. Fortunately, the present data did not exhibit any statistically significant heterogeneity.

In conclusion, the result of this combined meta-analysis comparing the treatment efficacies of alectinib and crizotinib showed that PFS was significantly greater in patients who received alectinib than in those who received crizotinib. Our results confirm the hypothesis that alectinib is more effective than crizotinib, with regard to PFS, in patients with previously untreated ALK-positive advanced NSCLC. However, there is an unmet medical need to identify subpopulations that might benefit from alectinib. Further detailed analyses are warranted to clarify the efficacy and safety of alectinib for the treatment of previously untreated ALK-positive advanced NSCLC.

Conflict of interest disclosure

None of the authors have any conflicts of interest to declare.

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