Clinical Outcomes of Crizotinib in ALK+ Non-small Cell Lung Cancer with Brain Metastasis: A Meta-Analysis

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ABSTRACT

Brain metastasis of non-small cell lung cancer (NSCLC) is commonly associated with mortality[1]. Rearrangement of anaplastic lymphoma kinase (ALK) has been implicated in the development of various cancers, including NSCLC[2]. Crizotinib, a tyrosine kinase inhibitor, has demonstrated efficacy in treating ALK-positive NSCLC, leading to prolonged progression-free survival[2,3]. To investigate the impact of crizotinib in NSCLC patients with brain metastasis, meta-analysis was performed using published clinical outcomes of NSCLC with brain metastasis treated with crizotinib. Studies of clinical efficacy of crizotinib on NSCLC were collected through PubMed. Three studies were included after screening for studies with similar methodologies. Meta-analysis was conducted using Review Manager 5. Preliminary data supports that ALK-positive patients are more likely to develop brain metastases, with an odd ratio of 1.80 [1.27, 2.56], p=0.001. Crizotinib appears to result in longer progression-free survival in one study, with a hazard ratio of 6.45 [2.80, 14.88], but it was found that crizotinib has limited effect in another study, with a hazard ratio of 0.88 [0.22, 3.50]. In addition, preliminary data supports that new brain metastases may develop in ALK+ NSCLC patients undergoing crizotinib treatment, ranging from 35-39% of patients. While it has been established that crizotinib is effective in treating ALK+ NSCLC, its role in brain metastasis appears to be limited. Results suggest that new therapeutical approaches might be needed in treating these patients.

INTRODUCTION

Non-Small Cell Lung Cancer (NSCLC) remains a leading cause of death in cancer patients, and brain metastases is implication of poor prognosis. Anaplastic lymphoma kinase (ALK) rearrangements has been identified in many NSCLCs and implicated as a potential target for small molecule inhibitors such as crizotinib[2,3,4]. However, the treatment of brain metastasis in advanced NSCLC remains a challenge due to blood brain barrier[5]. Currently it is yet to be determined whether crizotinib can extend the progression free survival in ALK+ NSCLC with brain metastases. This study is designed to investigate whether crizotinib is effective in treating NSCLC with brain metastasis.

METHODS

Meta-analysis was performed using published clinical outcomes of NSCLC with brain metastasis treated with crizotinib. Identification and screening are outlined in Figure 1. Meta-analysis was conducted using Review Manager 5.

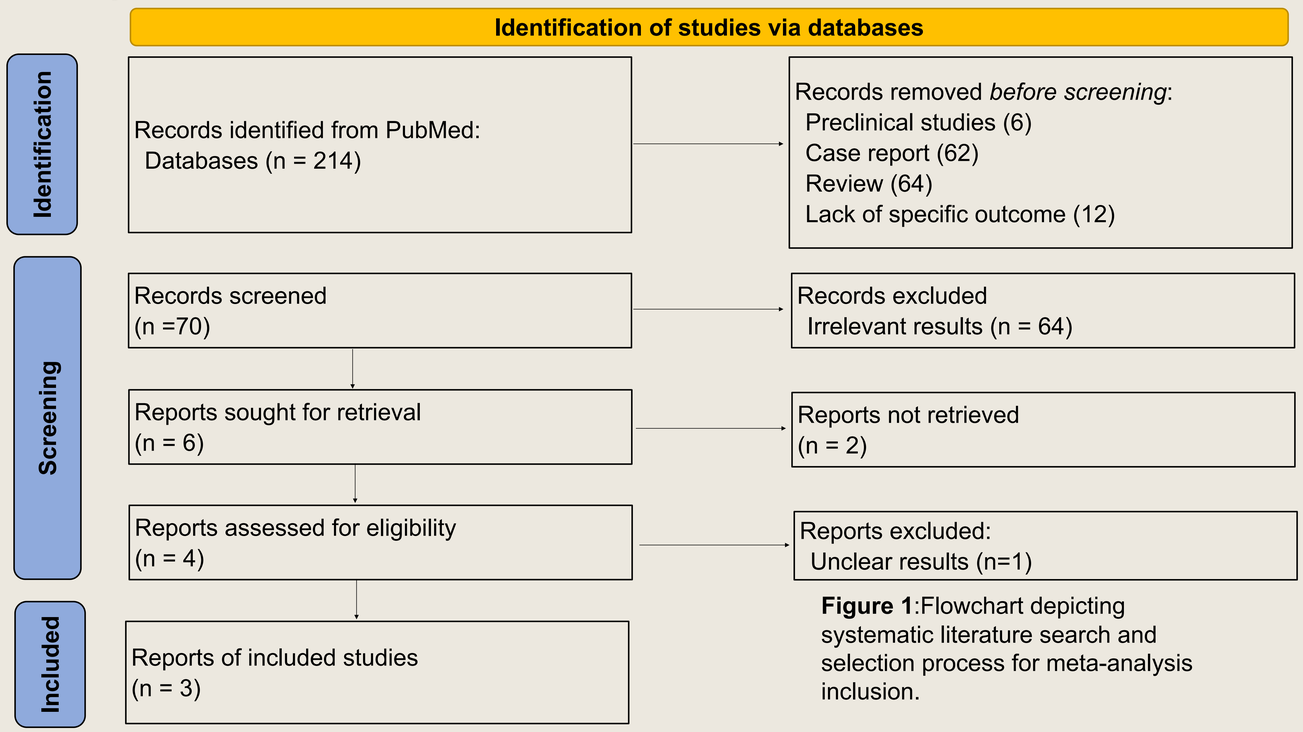

Figure 1:Flowchart depicting systematic literature search and selection process for meta-analysis inclusion.

RESULTS

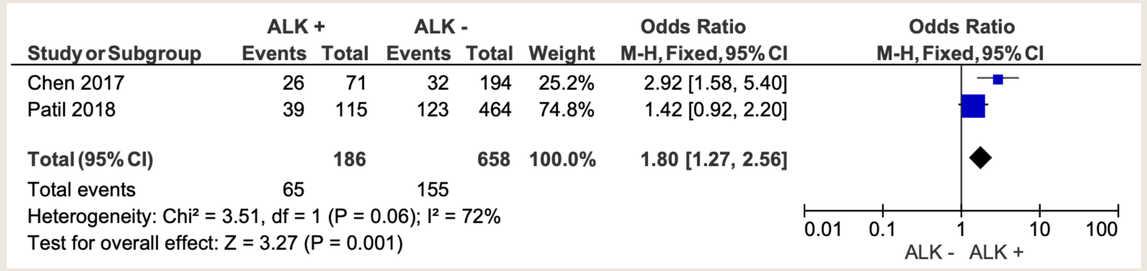

Figure 2: Association between NSCLC ALK (+/-) status and the risk of developing brain metastasis. The Odd ratios (OR) is 1.80 [1.27, 2.56] (95% CI), with a statistically significant effect (Z = 3.27, P = 0.001).

Table 1: Incidence of new brain metastases in ALK-positive NSCLC patients treated with crizotinib

Study	ALK+ Patients (n)	Patients Developing New Brain Metastases (n)	Incidence (%)
Patil et al. (2017)	56	22	39.3
Chen et al. (2017)	71	25	35.2

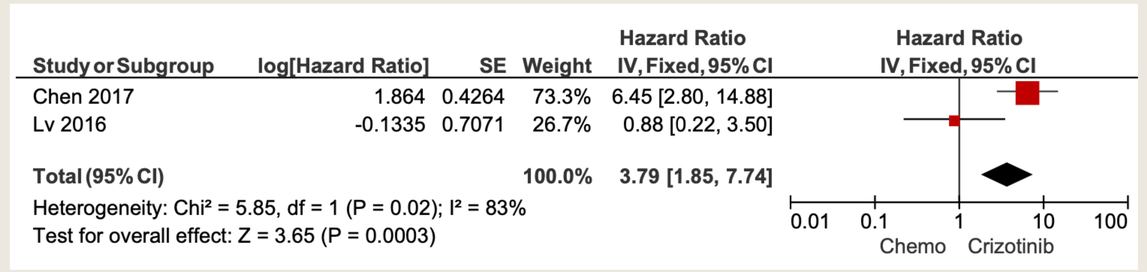

Figure 3: Progression-free survival in ALK+ patients with brain metastasis treated with crizotinib and chemotherapy. The hazard ratios is 3.79 [95% CI], Z = 3.65 (P = 0.0003).

DISCUSSION

- Brain metastasis is commonly seen in NSLCL, but more commonly in ALK+ patients.
- New metastasis to brain can occur during crizotinib treatment.
- Crizotinib appears to prolong PFS in NSCLC patients with brain metastasis, but interobserver variability is significant.

REFERENCES

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