Clinical Efficacy of Crizotinib as the First-Line Therapy of Advanced Non-Small-Cell Lung Carcinoma with ROS-1 Rearrangement: A Systematic Review

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INTRODUCTION

Lung cancer is still one of the most prevalent and deadly cancers globally [1]. Based on histopathology, lung cancer was classified into two groups, non-small cell lung carcinoma (NSCLC) and small cell lung carcinoma (SCLC), with NSCLC being the most frequent. Therapeutic approaches of NSCLC were classically utilized chemotherapy, surgery, and radiotherapy [2]. Compared to the old one, targeted therapy has led to a better prognosis for the patient after identifying an oncogenic driver, one of which is the c-ros oncogene-1 (ROS-1) mutation [3].

The prevalence of ROS-1 is nearly 1-2% among NSCLC, especially in the Asian population, with 3.33% in lung adenocarcinoma [3]. ROS-1 is an insulin receptor tyrosine kinase and has a homologous structure with anaplastic lymphomakinases (ALK) with more than 64% sequence in the kinase domain and 84% homology within the ATP binding site [4-6]. This finding could raise the possibility of applying the ALK inhibitor in ROS-1 rearrangements NSCLC.

ROS-1 NSCLC were currently treated with two agents such as entrectinib and ceritinib. Entrectinib was known to be effective through STARTRK-1, STARTRK-2, and ALKA-372-001 clinical trials [7,8] and became the current first-line therapy against ROS-1 rearrangement and was approved by the Food and Drug Administration (FDA). Furthermore, ceritinib is also chosen as the first line in ALK rearrangement and is preferred for advanced diseases [9].

Crizotinib is a drug designed to treat NSCLC with ALK mutation and has shown improvement in previous studies [10]. Crizotinib is approved as a therapy option for ROS-1 rearrangement in many countries, especially in advanced non-small-cell lung carcinoma [11,12]. Despite crizotinib efficacy, available studies did not...
analyze first-line crizotinib with chemotherapy. In addition, no reviews have assessed available studies to determine the efficacy and safety of first-line crizotinib against advanced NSCLC with ROS-1 rearrangement.

In this systematic review, the researchers identified the clinical and safety of profile crizotinib from available research as the first-line therapy in NSCLC with ROS-1 rearrangement. This paper could hopefully give an insight into the current evidence of crizotinib use in ROS-1 rearrangement among NSCLC patients for further studies.

METHODS

Eligibility criteria

This systematic review focused on the available observational study (clinical, prospective, and retrospective studies) that discussed the clinical efficacy of first-line crizotinib, evaluating the clinical efficacy as the primary outcome and followed by safety (adverse event) as the secondary outcome. The clinical efficacy was measured using Response Evaluation Criteria in Solid Tumor (RECIST), including complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), disease control rate (DCR), and objective response rate (ORR) along with prognosis indicators (progression-free survival and overall survival rate). DCR was defined as patients with CR or PR, whereas ORR was defined as those who showed CR, PR, and SD. Our study protocol followed the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) (Figure 1).

Studies were eligible if the subjects used crizotinib as the first-line monotherapy in patients with ROS-1 rearrangement in NSCLC without defining its histopathology type and reporting its efficacy against the patients. We analyze first-line crizotinib with chemotherapy. In addition, no reviews have assessed available studies to determine the efficacy and safety of first-line crizotinib against advanced NSCLC with ROS-1 rearrangement.

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also excluded the paper with (1) other cancer types (other solid tumor or hematological tumor) or other lung cancer types (small cell lung carcinoma (SCLC), (2) combination therapy of crizotinib, (3) case reports, (4) experimental studies, (5) reviews, and (6) conferences or proceeding papers, or other informal sources.

Search Strategies
The researchers conducted the literature search in January 2022 from PubMed, The Cochrane Library, EBSCOHost, and ScienceDirect using the keywords of (Crizotinib AND First-line AND (non-small cell lung cancer OR NSCLC OR non-small-cell lung carcinoma) AND ROS-1).

Selection of studies
Observational studies discussed the first-line crizotinib in NSCLC with ROS-1 rearrangements. The title and abstract were screened then the duplicates were removed. Full-text reading excluded articles that did not use the best patients’ response, PFS, and OS to measure clinical efficacy.

Data Extraction
The researchers extracted the information as follows: (1) Study design, (2) Genetic Alterations, (3) Detection methods, (4) Patients’ characteristics, (5) Oncology profile (subtypes and brain metastasis), (6) Level of Evidence, (7) Median follow-up, (8) Median PFS, (9) Median OS, and (10) Patients’ Best Response using RECIST (complete responses, partial response, stable disease, progressive disease, disease control rate, and objective response rate).

RESULTS
Search Results
The entire selection diagram was depicted on the flow diagram of PRISMA 2020 (Figure 1). The studies with relevant titles were selected with duplicates removed. Furthermore, the studies applied inclusion and exclusion criteria based on the desired outcome. The four studies were selected to be included in this paper, and the entire characteristic studies were summarized in Table 1 [13–16].

Out of 91 articles electronically searched, four observational studies comprising 310 patients were included, extracted, and summarized descriptively. All included studies were recruited advanced-stage NSCLC treated with first-line therapy. Three of the four papers were retrospective observational studies, with only one prospective study. Only two papers mentioned the regimen used for patients, crizotinib 250 mg twice daily. Entire studies recruited advanced-stage patients. Treatment efficacy was evaluated using Response Evaluation Criteria in Solid Tumor Classification (RECIST), overall survival rate (OS), and progression-free survival (PFS). Four included studies were conducted in China.

Outcome: Efficacy and analysis subgroup of selected studies
Entire studies were reported ROS-1 fusion alterations, which summarized in Table 2. Despite the unavailability of extracted PFS, DCR, and ORR from the Zhang Y et al. study, the mean follow-up duration varied, ranging from 24.9 months to 29.0 months. The median PFS and OS showed differences among studies. The median PFS, respectively, was 14.9, 23, 18.4, and 18.0 months for Xu et al. [13], Zheng et al. [14], Shen et al. [15], and Zhang et al. [16] The OS displayed similarity in Xu et al. [13], and Shen et al. [15] were Not Reach (NR). Only Zheng et al. [14] study found the median OS was 60.0 months. The proportion of patients’ best response was predominately found in the PR group in each study [84%, 57.1%, and 83.3%, among Xu et al. [13], Zheng et al. [14], and Shen et al. [15], respectively]. Furthermore, the included studies reported DCR above 90%, with three studies finding ORR above 80%.

Outcome: Safety of First Line Crizotinib
Only one study reported crizotinib’s safety or Adverse Event (AE) as the first-line therapy written by Shen et al. [15] The common side effects were grade 1 or 2 (15/30 patients) with alanine aminotransferase (ALT) elevation (53.3%), followed by aspartate aminotransferase elevation (43.3%) and nausea (36.7%). Five recruited patients performed dose reduction or temporary interruption caused by AE grade 3 or 4.

DISCUSSION
Evidence-based Medicine (EBM) aims to find and use the evidence in clinical settings for the best outcome. Physicians that treat lung cancer need to find the best available evidence with the best evidence, ranging from clinical trials to observational studies. This systematic review summarizes the current—the best evidence—research regarding the efficacy of the first-line crizotinib therapy in NSCLC with ROS-1 rearrangement [17,18].

The poor prognosis of advanced lung cancer patients demands therapy that could significantly improve the patient’s outcome, such as targeted therapy. Crizotinib is designated for ALK, MET, and ROS-1 rearrangements patients. For instance, the previous clinical trial, METROS [19], EUCROSS [20], AcSe [21], PROFILE 1001 [22], and the East-Asian trial [23], have concluded that crizotinib effectively improved patients’ prognosis compared to chemotherapy.

Despite the evidence of crizotinib superiority against currently recommended chemotherapy for treating ROS-1 fusion NSCLC, first-line crizotinib has not remained
Table 1. Characteristics of four Included Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Study Design</th>
<th>Genetic Alteration</th>
<th>Chemotherapy</th>
<th>Crizotinib regimen</th>
<th>Patients</th>
<th>Mean/median age (years)</th>
<th>M:F Ratio</th>
<th>Histopathology (%ADC)</th>
<th>Brain Metastatic (%)</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xu H</td>
<td>China</td>
<td>Retrospective, Multicenter</td>
<td>ROS1 fusion</td>
<td>Platinum-based doublet, maintenance bevacizumab and/or pemexatred</td>
<td>250 mg, 2x/day</td>
<td>56</td>
<td>53</td>
<td>15:41</td>
<td>98.2</td>
<td>19.6%</td>
<td>3</td>
</tr>
<tr>
<td>Zheng J</td>
<td>China</td>
<td>Retrospective, Multicenter</td>
<td>ROS1 fusion</td>
<td>NA</td>
<td>NA</td>
<td>56</td>
<td>NA</td>
<td>25:31</td>
<td>91.1</td>
<td>19.6%</td>
<td>3</td>
</tr>
<tr>
<td>Shen L</td>
<td>China</td>
<td>Prospective, Single center</td>
<td>ROS1 fusion</td>
<td>Pemexatred-carboplatin/cisplatin with/without bevacizumab</td>
<td>NA</td>
<td>30</td>
<td>51.5</td>
<td>3:7</td>
<td>100</td>
<td>30%</td>
<td>3</td>
</tr>
<tr>
<td>Zhang Y</td>
<td>China</td>
<td>Retrospective, Multicenter</td>
<td>ROS1 fusion</td>
<td>Pemexatred-carboplatin, docetaxel-cisplatin</td>
<td>250 mg, 2x/day</td>
<td>168</td>
<td>52</td>
<td>61:98</td>
<td>99.0</td>
<td>43%</td>
<td>3</td>
</tr>
</tbody>
</table>

Table 2. Efficacy of Crizotinib in patients with non-small-cell lung cancer with ROS1 rearrangements

<table>
<thead>
<tr>
<th>Study</th>
<th>Follow-up duration</th>
<th>Median PFS (months)</th>
<th>Median OS (months)</th>
<th>Patients Best Response (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CR</td>
</tr>
<tr>
<td>Xu H</td>
<td>24.9</td>
<td>14.9</td>
<td>NR</td>
<td>0</td>
</tr>
<tr>
<td>Zheng J</td>
<td>29.0</td>
<td>23.0</td>
<td>60.0</td>
<td>1.7</td>
</tr>
<tr>
<td>Shen L</td>
<td>28.1</td>
<td>18.4</td>
<td>NR</td>
<td>3.3</td>
</tr>
<tr>
<td>Zhang Y</td>
<td>28.0</td>
<td>18.0</td>
<td>NA</td>
<td>NA</td>
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robust. In the systematic review, crizotinib showed its efficacy in ROS-1 patients compared to the standard therapy. The previous three clinical trials, METROS [19], EUCROSS [20], and East-Asian [23], showed consistent DCR (85%, 90%, and 88.2%, respectively). The included studies in this review showed higher ORR than the previous trials, with only one study showing a similar ORR [13]. Survival outcomes were also improved and reported in previous studies.

Almost all subgroup analyses performed in each study revealed no significant difference with different factors being analyzed. Some factors need further exploration, such as fusions partner variation and the presence of brain metastasis.

The modified factors not discussed comprehensively in the included studies are the variations of ROS-1 fusion partners. For instance, Zheng et al. [14] reported that 24 concurrent mutations were detected. In addition, point mutation G2023R, a resistance mechanism, is found along with a novel point mutation L2026V. Furthermore, CD74-ROS-1 fusions have also been reported to improve PFS better than non-CD74-ROS-1 fusions, with a lower incidence of brain metastasis. Previous studies have elucidated that ROS-1 fusion with the concurrent mutation is also associated with a poorer prognosis, specifically TP-53 mutation [20]. Other mutations also have been known to affect crizotinib sensitivity, such as G2023R [24] and D2023R [25]. In brief, these concurrent mutations might infer patients’ prognosis and further need to be studied.

Metastasis could modify the patients’ outcomes when prescribed using crizotinib. Zhang et al. [14] found that patients with nonbrain metastasis baseline PFS were better than brain metastasis (22 months vs. 16 months, p=0.03, respectively).

Brain metastasis could also be linked to the concurrent mutation, for instance, CD74. CD74-ROS-1 fusion had a 31.6% central nervous system (CNS) mutation than the nonCD74-ROS-1. This finding contradicted Zhang et al. [14], which stated that there was no difference between groups. Furthermore, the previous study suggested that the proportion of intracranial progression in non-CNS metastasis baseline was higher in CD74-ROS-1 patients than in nonCD74-ROS-1 patients (33.3% vs. 21.4%, p=0.64, respectively). Both studies were the only report investigating the influence of concurrent mutation in ROS-1 patients and should be treated as hypotheses generated that need further exploration by further observational studies.

Safety profiles regarding crizotinib were less discussed in the presenting studies. Shen et al. [15] reported that the most frequent adverse event was grade 1 or 2, such as alanine aminotransferase elevation (53.3%), aspartate aminotransferase (43.3%), and nausea (16.7%). EUCROSS clinical trials [20] mainly reported AE 1 and 2 as the primary findings (94% and 65%, grade 1 and 2, respectively). These findings are also in line with entire previous clinical trials.

Some limitations were encountered that might affect the results. First, the subgroup analysis discussed in each paper was different, thus needing some standardization of modified factors that could affect the treatment response (baseline characteristics, crizotinib regimen, and the genetic event). All included studies came from the same country. It is not known whether race could affect treatment response. Second, the evidence of included studies was low; thus, higher-quality studies (double-blind, randomized controlled trials) were needed. Third, the participants included in each study were inadequate; even the results showed promising results.

CONCLUSIONS

This systematic review suggests the potency of the first line of crizotinib therapy in advanced NSCLC patients. Regarding the level of evidence and the limitation of the included studies, we recommend further higher quality in this scope to be held.

DECLARATIONS

Competing of Interest

The authors declare no competing interest in this study.

REFERENCES


