RESEARCH ARTICLE

A Pooled Analysis on Crizotinib in Treating Chinese Patients with EML4-ALK Positive Non-small-cell Lung Cancer

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Abstract

Background: This analysis was conducted to evaluate the efficacy and safety of crizotinib based regimens in treating Chinese patients with EML4-ALK positive non-small-cell lung cancer. Materials and Methods: Clinical studies evaluating the efficacy and safety of crizotinib based regimens on response and safety for Chinese patients with EML4-ALK positive non-small-cell lung cancer were identified by using a predefined search strategy. Pooled response rate (RR) of treatment were calculated. Results: In crizotinib based regimens, 3 clinical studies which including 128 Chinese patients with EML4-ALK positive non-small-cell lung cancer and treated with crizotinib based regimen were considered eligible for inclusion. Pooled analysis suggested that, in all patients, the pooled RR was 59.3% (76/128) in crizotinib based regimens. ALT/AST mild visual disturbances, nausea, and vomiting were the main side effects. No treatment related death occurred in these crizotinib based treatments. Conclusions: This pooled analysis suggests that crizotinib based regimens are associated with good response rate and accepted toxicities in treating Chinese patients with EML4-ALK positive non-small-cell lung cancer.

Keywords: crizotinib - second-line chemotherapy - EML4-ALK positive non-small-cell lung cancer

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Introduction

Lung cancer is a leading cause of cancer-related mortality worldwide (Herbst et al., 2008). According to an annual report of 2012 Chinese cancer registration , more than 3 million new cases of lung cancer will be diagnosed every year, and an approximately 2.7 million deaths from lung cancer will account for 13% of all mortalities with poor treatment results and prognosis (Ji et al., 2014; Cui et al., 2014; Huang et al., 2014; Fei et al., 2013). And in lung cancer, approximately 85-90% of patients are diagnosed with non-small cell lung cancer (NSCLC), which is the most common cancer worldwide. The incidence of NSCLC is still gradually increasing (Weinmann et al., 2003; Roberts et al., 2013). Patients with NSCLC are generally diagnosed with stage IIIB or stage IV disease. For patients newly diagnosed with advanced NSCLC, the median overall survival (OS) with platinum-based chemotherapy is 7.4-9.9 months, and the median OS with combined chemotherapy and bevacizumab is 12.5 months. Median progression-free survival (PFS) with second-line chemotherapy, such as pemetrexed and docetaxel, is approximately 2.2-2.9 months. Although associated with a higher response rate, OS with gefitinib is similar to that of standard carboplatin plus paclitaxel chemotherapy (Fukuoka et al., 2011). The 5-year survival rate of NSCLC is lower than 20% (Klastersky et al., 2001; American Cancer Society, 2011). However, despite the relatively poor prognosis for NSCLC patients, the development of treatments for NSCLC is a focus of research (Bowles et al., 2012).

In recent years, the identification of genetic abnormalities that may underlie oncogenic development and progression have revolutionized oncology research (Kanteti et al., 2014). A translocation in the gene encoding the receptor tyrosine kinase anaplastic lymphoma kinase (ALK), leading to the expression of ALK fusion proteins, was first reported in NSCLC patients in 2007 (Soda et al., 2007; Rikova et al., 2007). The activated ALK fusion proteins result in aberrant ALK signaling and oncogenic transformation through several molecular signaling pathways, including PI3K/AKT/mTOR, JAK/STAT, and RAS/MEK/ERK (Steuer et al., 2014 10). Constitutive ALK signaling mediates enhanced cell proliferation, cell survival, and metabolism. ALK gene rearrangements are found in approximately 2-7% of unselected patients with NSCLC (Miyanaga et al., 2013). Because of the role of ALK in oncogenesis, tyrosine kinase inhibition has been investigated as a therapeutic approach (Miyanaga et al., 2013). Crizotinib is a small-molecule selective inhibitor of ALK and mesenchymal epithelial growth factor / hepatocyte growth factor receptor kinases (Chen et al., 2013). It was approved via accelerated drug approval by the US Food and Drug Administration in 2011, based on the findings of two early phase clinical trials demonstrating prolonged progression-free survival and high response

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rates (50-57%) in patients with ALK-positive NSCLC (Berge et al., 2013; Kwak et al., 2010).

According to this background, we hypothesize that crizotinib originated regimen could be established as an optimal schedule in treating Chinese patients with EML4-ALK positive non-small-cell lung cancer.

Materials and Methods

Search strategy

We searched PUBMED, by using the following search terms: (non-small-cell lung cancer) and (crizotinib). All clinical studies evaluating the impact of crizotinib on the response or survival and side effects for chinese patients with non-small-cell lung cancer published in English prior to May 2015 were identified. If samples of two studies overlap, only the newest one was included. Additional articles were obtained from references within the articles identified by the electronic search. We did not consider meeting abstracts or unpublished reports.

Inclusion and exclusion criteria

We reviewed abstracts of all citations and retrieved studies. The following criteria were used to include published studies: (1) clinical studies, combined with cisplatin, carboplatin, or others; (2) The study was performed in accordance with the Helsinki Declaration (1964, amended in 1975 and 1983) of the World Medical Association. Eligibility criteria included histologically or cytologically verified non-small-cell lung cancer, the presence of at least one bidimensionally measurable lesion, a performance status (WHO) of less than 2. Studies were excluded if one of the following existed: (a) duplicate data; (b) no sufficient data were reported.

Data collection and analysis

Selection of trials and data extraction: The titles and abstracts of publications identified according to the above search strategy were assessed independently for inclusion by two authors, the full text was selected for further assessment if the abstract suggests relevance. Disagreement was resolved by discussion. Data was extracted by independent authors. The following recorded data were extracted: author, publication data, country of the first or corresponding author, the number of patients. Outcome presented in at least 3 studies were extracted for combined analysis.

Results

There were 810 papers relevant to the search words by the end of May 2015. Via steps of screening the title and reading the abstract, 3 studies were identified (Wu, et al., 2015; Cui et al., 2015; Cui et al., 2014). All these studies had been carried out in China. The following outcomes were presented in at least all studies and extracted for combined analysis: response rate, including the rate of complete or partial response (CR or PR) and toxicities. Characteristics of studies included in this analysis are presented as short-term outcomes: the response rate of Wu, et al. was 61.9% (13/21), of Cui et al. was 52.2 % (35/67), and of Cui et al. was 70 % (28/40). Totally, 128 patients were enrolled and 76 patients achieved CR or PR, the pooled response rate thus was 76/128 (59.3%). Major adverse effects were increased ALT/AST mild visual disturbances, nausea, and vomiting.

Discussion

Based on report from National Comprehensive Cancer Network guidelines, 4-6 cycles of platinum-based doublet chemotherapy is recommend as first-line treatment for patients with NSCLC (National Comprehensive Cancer Network et al., 2013). For those patients with an EGFR mutation or ALK rearrangement, use of a specific inhibitor directed at that target is indicated either as the initial treatment or as therapy when progressive disease develops.Currently the recommended second-line or third-line treatments for NSCLC patients include docetaxel, erlotinib, pemetrexed or gemcitabine (Leighl et al., 2012; Shepherd et al., 2000; Shepherd et al., 2005; Hanna et al., 2004). The platinum doublet generally consists of cisplatin or carboplatin with another cytotoxic agent, sometimes in combination with a biologic agent, e.g., bevacizumab (B). Combined chemotherapy in addition to cisplatin and carboplatin includes pemetrexed, taxanes (docetaxel, paclitaxel, nanoparticle albumin bound paclitaxel), gemcitabine, vinorelbine, and camptothecins (irinotecan, topotecan). The use of cytotoxic chemotherapy as the initial treatment for patients not selected based upon EGFR mutation status and for those whose tumors do not contain an EGFR mutation is supported by the results of the tarceva or chemotherapy trial (Gridelli et al., 2012). Patients in that trial were randomly divided into first-line erlotinib followed by chemotherapy (cisplatin plus gemcitabine) upon progression or the same first-line chemotherapy followed by erlotinib upon progression. OS was significantly longer in unselected patients assigned to initial chemotherapy followed by second-line erlotinib. For patients known to be EGFR mutation negative, OS was significantly longer with initial chemotherapy. Combination chemotherapy regimens using a platinum doublet result in median OS of 8-11 mo (Cappuzzo et al., 2010). Obviously, clinical outcomes in patients with NSCLC continue to be poor, with an OS of 7 to 9 months, and objective response rate of less than 10% (Hotta et al., 2007). Therefore, novel treatment strategies for advanced NSCLC patients failing the first-line therapies are urgently required.

Previous research to evaluate the therapeutic effects of different therapeutic regimens for non-small-cell lung cancer (NSCLC) with or without EML4-ALK rearrangement was conducted at the Department of Radiation Oncology, General Hospital of PLA, Beijing (Wu et al., 2015). In this study, they enrolled 21 ALK-positive and 50 ALK-negative NSCLC patients who received voluntarily EML4-ALK testing and 75 NSCLC patients without AL testing. And in this study, 3 groups of patients received different treatments, then therapeutic effects, and treatment-related adverse events were compared. This study reveled that Crizotinib treatment significantly prolonged the progression-free survival in

EML4-ALK-positive patients with an objective response rate of 61.9% and a median response duration of 16 months, which were significantly better than those in with ALK-negative patients and patients without ALK testing who received different second-line therapies. (Wu et al., 2015). In conclusion, Wu et al.suggested that Crizotinib is superior to platinum-based chemotherapy in NSCLC patients with ALK rearrangement. ALK rearrangement id not a modifier of the effect of chemotherapy regimens in NSCLC patients. (Wu et al., 2015). In a retrospective study by Cui et al., they analyzed 72 Chinese patients with ALK-positive, advanced NSCLC from June 1, 2013, to October 15, 2014 (Cui et al., 2015). All 72 patients received oral crizotinib 250 mg twice daily in 28-day cycles. In this study, tumor response was assessed after the first cycle of crizotinib and then after every two cycles using the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.0. Tolerability was assessed at least twice per cycle until crizotinib was discontinued. The patients tended to be young (mean age 55 years, range 31-83 years), never or light smokers (smoking index <400), and to have an adenocarcinoma histology. Most (49/72; 68.1 %) had received previous anticancer treatment before crizotinib therapy. Sixty-seven patients (93 %) were able to be assessed for efficacy. The objective response rate and disease control rate were 52.2 % (95%CI 40.5-63.9 %) and 64.2 % (95%CI 52.75-75.7 %), respectively. The estimated median progression-free survival for all 67 patients was 10.3 months (95%CI 8.6-12.0 months). Mild visual disturbances, nausea, vomiting, diarrhea and constipation were the most commonly reported adverse effects (Cui et al., 2015). In conculsion, crizotinib was well tolerated and showed promising efficacy in Chinese patients with ALK-positive, advanced NSCLC (Cui et al., 2015). In a study by Cao et al., they enrolled 40 patients with EML4-ALK positive advanced NSCLC (median age, 43 years) from May 2012 to Aug 2013 (Cao et al., 2014). In their results, they suggested that all 40 patients were evaluable for safety and efficacy, all patients had adenocarcinoma and stage IV disease, and 42.5% were female. Six patients received frontline treatment with crizotinib, 17 patients had 1 prior treatment, and 17 patients had more than 2 lines of prior treatment. Patients received a median of 5 cycles of treatment (range 1-15 cycles). After the first cycle, 92.5% (37/40) patients archived partial remission (PR). At the end of the follow-up period, the overall PR rate was 70% (28/40), and progression of disease (PD) occurred in 30% of patients (12/40). The median PFS was 28 weeks (95% CI 15.4 to 40.5 weeks), and median OS was 40 weeks (95% CI 38.6 to 49.3 weeks). The most frequent treatment-related AEs were vomiting (47.5%), vision disorder (27.5%) and increased ALT/AST (42%); most toxicities were Grade 1/2. Observed treatment-related Grade 3/4 AEs included increased ALT/AST (10%) and vomiting (5%). The EML4-ALK fusion rate and number of prior chemotherapy cycles did not appear to significantly affect the efficacy of crizotinib. However, PS 0-2 patients had improved PFS (50 weeks vs. 24 weeks, p=0.015) (Cao et al., 2014). Thus in conclusion, Cao suggested that Crizotinib was safe, well-tolerated, and effective in Chinese patients with pre-treated ALK-rearranged NSCLC. QOL was improved and PS appears to have an effect on the efficacy of crizotinib, but prior treatment and ALK fusion rate do not. (Cao et al., 2012).

Our current study was designed to evaluate the efficacy and safety of crizotinib based regimens in treating Chinese patients with EML4-ALK positive non-small-cell lung cancer. Our results demonstrated that when crizotinib based regimens was used as a palliative treatment, the pooled RR was 59.3% (76/128). ALT/AST mild visual disturbances, nausea, and vomiting were the main side effects. No treatment related death occurred in these crizotinib based treatments. In conclusion, our current systemic analysis suggests that crizotinib based regimens are associated with good response rate and accepted toxicities in treating Chinese patients with EML4-ALK positive non-small-cell lung cancer.

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