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Does crizotinib work better in reducing the chest pain of ALKpositive non-small cell lung cancer patients compared with chemotherapy?

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Abstract

Objective: The objective of this EBM review is to determine whether or not crizotinib works better in reducing the chest pain of *ALK*-positive non-small cell lung cancer (NSCLC) patients compared with chemotherapy.

Study Design: This paper evaluates three randomized controlled trials (RCTs), which were all published in peer-reviewed journals in English after 2013.

Data Sources: Three RCTs comparing the efficacy of crizotinib in reducing the chest pain in *ALK*-positive non-small cell lung cancer patients with chemotherapy including pemetrexed and docetaxel. Articles were selected via PubMed based on the outcomes of the studies mattered to patients (POEM).

Outcomes Measured: The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire 13-item lung cancer module (EORTC QLQ-LC13) was completed by patients, the scores were used to measure lung cancer specific symptoms including chest pain.

Results: All the three RCTs articles (Shaw 2013, Solomon, 2014, Blackhall 2014) showed that crizotinib is more effective in decreasing the chest pain in *ALK*-positive NSCLC patients than chemotherapy ($P<0.001$ [pemetrexed or docetaxel], $P<0.001$ [pemetrexed], $P<0.05$ [pemetrexed] and $P<0.001$ [docetaxel]). All these studies suggest that crizotinib is superior to chemotherapy (pemetrexed or docetaxel) in reducing chest pain for *ALK*-positive NSCLC patients.

Conclusions: The data analysis of these studies indicates crizotinib works better in reducing the chest pain in *ALK*-positive NSCLC patients compared with chemotherapy including pemetrexed and docetaxel. The studies are limited to *ALK*-positive NSCLC patients. The treatments in the studies are not double-blinded, chest pain could be caused by other factors such as anxiety, which were not evaluated in this study.

Key Words: crizotinib, *ALK*-positive NSCLC, chest pain, chemotherapy.

Introduction

The cell is the basic unit in the human body, it normally goes through growth, proliferation, differentiation, and death. When a series of genetic changes occur in the cells, they gain the ability to escape from the cell division and cell death control. Uncontrolled cell growth could form a tumor (solid tumor) or generate many immature cells (liquid tumor). Cancer occurs when the tumor becomes invasive and spreads to nearby tissues or even distant organs. Cancer cells affect the normal organs function, eventually cause organ failure and death.

Cancer can occur almost anywhere in the body. Lung cancer is an abnormal overgrowth of lung tissue cells, may spread to lymph nodes and other organs such as the liver, brain, or bone. Small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC) are two major types of lung cancer.[1] More than 80% of lung cancers are NSCLC which includes adenocarcinoma, squamous cell carcinoma, and large cell carcinoma.[1] Adenocarcinoma is the most common form of lung cancer in the United States for both men and women which arises from the glandular tissue that lines inside of the lung.[1] Anaplastic lymphoma kinase (*ALK*) gene encodes *ALK* receptor tyrosine kinase which actives a signaling pathway that plays an important role in regulating cell growth.[2,3] *ALK* gene mutation involved NSCLC is called *ALK*-positive NSCLC. The majority of *ALK*-positive NSCLC patients are young, female, and normally diagnosed before 50.[4] The most common risk factor for NSCLC is smoking, however, *ALK*-positive NSCLC was found to have no strong association with smoking or environmental toxins.[4]

Lung cancer is the 2nd most common cancer and the leading cause of cancer death in both men and women in the United States.[5] The Centers for Disease Control and Prevention (CDC) statistical study shows 218,229 new cases of lung cancer in the United States in 2016.[6] NSCLC is accounting for 85% of all lung cancer, and about 1 of 25 NSCLC patients is *ALK*-positive

NSCLC.[7,8] The national expenditure of NSCLS was approximately $13.6 billion in the United States in 2016.[9] The American Cancer Society estimates about 228,150 new lung cancer cases and about 142,670 deaths from lung cancer in 2019 in the United States.[5]

Early stage lung cancer is normally asymptomatic; the symptoms in advanced lung cancer include cough, coughing up blood, shortness of breath, unintentional weight loss, chest pain, hoarseness, bone pain, and headache.[10] The chest pain is one of the most common symptoms.

Surgery is the standard treatment for localized NSCLC; radiation therapy is usually used before surgery to shrink lung tumor or after surgery to kill any possible missed tumor.[11] Combination platinum-based chemotherapy such as carboplatin and paclitaxel or carboplatin and pemetrexed are commonly used for locally advanced NSCLC, metastatic NSCLC, or after surgery.[12] Chemotherapy generally targets fast-growing and dividing cells which is not specific and works throughout the body. In the past decade, targeted therapies are used to treat patients based on the characteristics of the tumor, molecular tests are used to determine the gene mutations or rearrangements and guide the treatment.[13] Another cancer treatment approach, called immunotherapy or biologic therapy, is used to boost the body's immune system to fight cancer cells.[14]

Crizotinib is the first targeted therapy drug designed for *ALK*-positive NSCLC by targeting both *MET* and *ALK* receptor tyrosine kinases.[15] Studies have shown crizotinib significantly increases progression-free survival time in *ALK*-positive NSCLC patients compared with chemotherapy (pemetrexed and docetaxel).[16,17,18] As the progression-free survival time in *ALK*-positive NSCLC patients prolonged in crizotinib treatment group, it is reasonable to predict that crizotinib improves key lung-cancer symptoms (cough, dyspnea, chest pain, and fatigue) and overall quality of life as well.

Objective

The objective of this systematic review is to determine whether or not crizotinib works better in reducing the chest pain of *ALK*-positive non-small cell lung cancer patients compared with chemotherapy.

Methods

This paper evaluates three randomized controlled trials comparing the efficacy of crizotinib in reducing the chest pain in *ALK*-positive non-small cell lung cancer patients with chemotherapy.

The patients of the review are the age of 18 years or older with locally advanced or metastatic NSCLC that was positive for an *ALK* rearrangement.[16,17,18] The Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 was used to evaluate the patients, characteristics of the patients include age, sex, race, smoking status, histology of disease, Eastern Cooperative Oncology Group performance status, extent of disease, and brain metastases.[19] Two comparison groups of patients are evaluated, one never had chemotherapy and another group had one prior platinum-based chemotherapy regimen. In this review one of the most common lung cancer symptoms — the chest pain — is primarily evaluated by comparing crizotinib treatment or chemotherapy.

The three randomized controlled trials (RCTs) for this review were searched via PubMed, the articles were selected based on the outcomes of the studies mattered to patients (POEM). All the articles were published in peer-reviewed journals and written in English. Other criteria for the studies include RCT studies published after 2013 and the exclusion of non-*ALK*-positive NSCLC or SCLC patients. Keywords used in searching the articles are: crizotinib, *ALK*-positive NSCLC,

chest pain, and chemotherapy. Summary of statistics was reported as mean, SD, and p-value. Demographics and characteristics of this study are as follow (Table 1):

Table 1. Demographics and Characteristics

Study	Type	# Pts	Age (yrs)	Inclusion Criteria	Exclusion criteria	W/D	Interventions
Shaw, 2013 (1)	RCT	347	22-85	Pts with *ALK*-positive NSCLC who had received one prior platinum-based regimen.	Pts with *ALK*-positive NSCLC who had received no previous systemic treatment.	180	Chest pain was evaluated using EORTC QLQ-LC13 module and compared between crizotinib treatment and chemotherapy treatment.
Solomon, 2014 (2)	RCT	343	19-78	Pts with *ALK*-positive NSCLC who had received no previous systemic treatment.	Pts with *ALK*-positive NSCLC who had received one prior platinum-based regimen.	180	Chest pain was evaluated using EORTC QLQ-LC13 module and compared between crizotinib treatment and chemotherapy treatment.
Blackhall, 2014 (3)	RCT	344	22-81	Pts with *ALK*-positive NSCLC who had received one prior platinum-based regimen.	Pts with *ALK*-positive NSCLC who had received no previous systemic treatment.	17	Chest pain was evaluated using EORTC QLQ-LC13 module and compared between crizotinib treatment and chemotherapy treatment.

Outcomes Measured

In this review, the primary focus of the outcome was the reduction of chest pain in *ALK*-positive NSCLC patients with crizotinib treatment or chemotherapy. The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire 13-item lung cancer module (EORTC QLQ-LC13) was completed by patients, the scores were used to measure lung cancer specific symptoms including chest pain.[16,17,18] Patient-reported outcomes of the chest pain had a baseline assessment and at least one post-baseline assessment.[16,17,18] The chest pain could also be caused by other factors such as anxiety or depression, which were not evaluated in this study. The progression-free survival time was evaluated and will not be discussed in this study.

Results

An open-label, phase 3 trial study conducted by Shaw et al. with 347 *ALK*-positive NSCLC patients who had received one prior platinum-based regimen were randomly assigned to receive crizotinib (250 mg, twice daily) or intravenous chemotherapy – pemetrexed (500 mg per square meter of body surface area) or docetaxel (75 mg per square meter).[16] Among the 347 patients, 173 of them received crizotinib and 174 received chemotherapy.[16] Patients in the chemotherapy group were allowed to cross over to crizotinib as part of a separate study.[16]

Questionnaires including EORTC QLQ LC-13 to measure patient-reported outcomes (PRO) were given at day 1 as the baseline and at every 3-week subsequent cycle, the primary end point was progression-free survival (PFS).[16] The chest pain is one of the items in EORTC QLQ LC-13. PROs were evaluated in patients with a baseline assessment and at least one post treatment assessment using repeated-measures mixed-effects modeling to compare crizotinib group and chemotherapy group by the overall change from baseline scores on EORTC QLQ LC-13.[16] The

raw scores were standardized into a range from 0-100 with 100 presenting the highest symptom severity, every 10 points change from baseline consider as clinically meaningful.[20] The mean reduction in symptom score was measured, the chest pain has a significantly greater reduction from the baseline in crizotinib group than in chemotherapy group with patients who had one prior platinum-based regimen (P<0.001; Table 2).[16]

Table 2. Overall change from baseline in the chest pain.

	Crizotinib	Chemotherapy
Mean change from baseline P<0.001	-12	2

Another similar study was conducted by Solomon et al.; 343 *ALK*-positive NSCLC patients who had no previous systemic treatment were randomized to receive crizotinib (250 mg, twice daily) or intravenous chemotherapy (pemetrexed, 500 mg per square meter of body surface area, plus either cisplatin, 75 mg per square meter, or carboplatin, target area under the curve of 5-6 mg per milliliter per minute).[17] Total 172 of the patients were in crizotinib group, and 171 of them were in chemotherapy group. Crossover to crizotinib treatment from chemotherapy group was allowed if disease progressed.[17] Measurement and data analysis for the chest pain in two different groups were similar to the first study. The overall change from baseline for the chest pain has a great reduction in the crizotinib group than in the chemotherapy group with patients had previous systemic treatment (P<0.001; Table 3).[17]

Table 3. Overall change from baseline in the chest pain.

	Crizotinib	Chemotherapy
Mean change from baseline P<0.001	-9	0

The last study by Blackhallet al. included 344 *ALK*-positive NSCLC patients who had received one prior platinum-based regimen.[18] Patients were randomly assigned to receive crizotinib (173 patients, 250 mg, twice daily) or intravenous chemotherapy (171 patients, pemetrexed: 500 mg per square meter or docetaxel: 75 mg per square meter) in a 1:1 ratio.[18] No cross over in the two groups were permitted.[18]

The scores of questionnaires EORTC QLQ LC-13 were measured and standardized using the same methods as the last two studies.[18] The scores were compared between the crizotinib group and each of the chemotherapy subgroups (pemetrexed and docetaxel) in: 1. mean change from baseline; 2. the proportion of patients with improved or worse outcomes.[18] Docetaxel and pemetrexed were associated with a significant worsening of chest pain in comparing with crizotinib (P<0.001; Table 4).[18] In Table 4, a score difference of less than zero indicated crizotinib favors reduced chest pain, while a score of greater than zero indicated chemotherapy resulted in less chest pain, and zero value means no difference between crizotinib and chemotherapy. The chest pain was also found to improve in more patients on crizotinib group than on chemotherapy group (P<0.001, P<0.05; Table5).[18]

Table 4. The estimated difference for chest pain symptoms in the crizotinib group vs. the chemotherapy group.

	Crizotinib vs. Pemetrexed	Crizotinib vs. Docetaxel
Estimated diff. of Chest Pain	-12.54 (-16.71 to -8.37) (95% CI, P<0.001)	-14.36(-21.18 to -7.53) (95% CI, P<0.001)

Table 5. The proportion of patients with improvement and worsening in chest pain in the crizotinib group vs. chemotherapy group.

Chest Pain	Crizotinib	Pemetrexed	Docetaxel
Improvement Rates (P<0.001)	40%	28%	15%
Worsening Rates (P<0.05)	8%	21%	39%

Discussion and Conclusion

For advanced NSCLC, palliation of symptoms and improvement in health-related quality of life are more important when the disease is incurable. Chest pain is one of the major symptoms of any kind of lung cancer. Platinum-based double-agent chemotherapy was generally the standard treatment for NSCLC.[21] Crizotinib is the first targeted therapy drug designed for *ALK*-positive NSCLC.[15] Studies indicated in *ALK*-positive NSCLC patients crizotinib was significantly greater in reducing lung cancer symptoms including chest pain comparing with chemotherapy, which is independent of the type of chemotherapy (pemetrexed or docetaxel), the performance status of the patients, the race of patients, the presence or absence of brain metastases, and previous systematic treatment or not.[16,17,18] Crizotinib treatment also resulted in longer PFS, greater improvement in global quality of life, but overall survival did not have significant change between crizotinib and chemotherapy.[16,17]

The EORTC tools used in these studies were previously validated to be clinically significant when there is a 10-point or greater change, the chest pain improvement reported from these studies are highly clinically relevant.[18] The significant improvement of chest pain, as well as general health status, were observed in crizotinib treatment, but not in either type of chemotherapy.[16,17,18] It is debatable that the outcome report was based on patients' reports but not physicians, also patients with the disease were possible more adapted to the symptoms. All these studies are open-label trials which could potentially cause patients' bias in their self-report outcomes based on the different treatment expectation. Different compliance between the two treatment groups could also be another limitation.

In conclusion, crizotinib demonstrates consistent improvement compared with chemotherapy (docetaxel or pemetrexed) in chest pain and other key lung cancer symptoms, as well as on the global quality of life and general health status. As an inhibitor of *Met* and *ALK*, crizotinib has the potential to treat different types of cancers which contain *Met* or *ALK* mutations such as colorectal cancer, liver cancer, or gastric carcinoma. Further research can include the study of how effective crizotinib is in other type of cancers treatment.

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