Original Article
Gefitinib and docetaxel for the treatment of non-small cell lung cancer: a meta-analysis

Huiqing Yu¹, Aihong Zhang²

¹Department of Oncology, Chongqing Cancer Hospital, Chongqing 102206, P. R. China; ²Department of Pharmacy, The Cancer Hospital Affiliated to Harbin Medical University, Harbin 150086, P. R. China

Received April 19, 2016; Accepted September 25, 2016; Epub November 15, 2016; Published November 30, 2016

Abstract: To systematically evaluate the efficacy and safety of gefitinib and docetaxel in the treatment of non-small cell lung cancer. We searched the Cochrane Library (1993~2015.10), PubMed (1970~2015.10), CBM (1978~2015.10), CNKI (1996~2015.10), Wanfang Data (1999~2015.10), VIP database (1996~2015.10) and Google scholar by a computer, and manually searched relevant journals. The comparison between randomized controlled trials (RCTs) of gefitinib (treatment group) and docetaxel (control group) in the treatment of non-small cell lung cancer were collected. The data were independently extracted by two researchers according to inclusion and exclusion criteria. After evaluation of the research quality according to the Cochrane Handbook for Systematic Reviews of Interventions version 5.0, meta-analysis was performed for the included literatures by RevMan 5.2 software. A total of 14 RCTs were included. Meta-analysis indicated that, compared to docetaxel, gefitinib could improve the total efficiency (RR=1.40, 95% CI (1.18, 1.65), P<0.0001) and the trial outcome index (TOI) improvement rate (RR=1.89, 95% CI (1.56, 2.29), P<0.00001), and decrease the incidence of neutropenia (RR=0.16, 95% CI (0.07, 0.36), P<0.00001) of non-small cell lung cancer patients. However, in terms of 1-year survival rate and disease control rate, there was no statistically significant difference (P>0.05). Compared to docetaxel, gefitinib shows more advantages. However, more high-quality studies are still required to verify its effectiveness and safety.

Keywords: Gefitinib, docetaxel, non-small cell lung cancer, randomized controlled trial, meta-analysis

Introduction
Lung cancer is one of the diseases seriously threaten human health, and the leading cause of cancer death [1]. According to the degree of differentiation and morphological characteristics of each type of lung cancer, it is currently divided into two categories, i.e. non-small cell lung cancer (NSCLC) and small lung cancer (SCLC). NSCLC accounts for 80% of lung cancer and included squamous cell carcinoma, adenocarcinoma, and large cell carcinoma [2]. For the NSCLC patients, more than half of them are diagnosed with advanced stage and lost the chance of operation [3].

Chemotherapy is still the most important treatment, which can prolong the survival time of part of the patients with advanced stage and recurrent lung cancer, and improve their quality of life [4]. Currently, combination of platinum drugs with the third generation chemotherapy drug gemcitabine (GP program) has become the standard first-line treatment of patients with advanced NSCLC [5]. However, the total efficiency and 1-year survival time of the GP program is still not satisfactory in the treatment of NSCLC, and its adverse reactions, such as thrombocytopenia and anemia, affect the compliance of patients [6].

Studies found that docetaxel showed more advantages in the treatment of lung cancer [7-9]. Therefore, American Society of Clinical Oncology (ASCO) recommends that docetaxel and pemetrexed can be used in chemotherapy if the patients still have a good performance status after failure of the first-line chemotherapy [10]. With the development of molecular targeted drugs, the treatment of NSCLC has a new breakthrough. Gifitinib (trade name Iressa) is an anilinoquinazoline compound and an oral epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI), which can inhibit the activation of EGFR, and thus inhibit cell cycle progression, accelerate cell apoptosis,
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inhibit angiogenesis and inhibit tumor cell invasion and metastasis [11-13]. It has currently been used in clinic [14], but still has a lot of controversy compared with the traditional chemotherapy drugs docetaxel [15]. Therefore, we collected the published comparison between the randomized controlled trials (RCTs) of gefitinib and docetaxel in the treatment of NSCLC, and analyzed the efficacy and safety of gefitinib in the treatment of NSCLC using Cochrane systematic reviews.

Materials and methods

Inclusion and exclusion criteria

Type of study: RCTs, whether allocation concealment and blinding were used or not, were included. The research articles were full texts in Chinese or English.

Study object

Patients should meet the following criteria: clearly diagnosed as NSCLC by biopsy; received at least one course of chemotherapy, and their liver and kidney function, hematology and electrocardiogram had no obvious abnormalities; never received prior chemotherapy of any one of the two drugs as single or combination; whether had surgery was not considered; whether had tumor distant metastasis was not considered; race, age, sex and course of disease were not limited.

Intervention measures

Gefitinib was used for the treatment group and could be combined with conventional chemotherapy, while docetaxel was used for the treatment of the control group with other interventions consistent with the treatment group. The dosages and periods of treatment by gefitinib and other drugs were not limited.

Outcome measures

Main measures: 1-year survival rate, overall response rate (ORR), disease control rate (DCR), trial outcome index (TOI) improvement rate and incidence of neutropenia.

Document retrieval

The Cochrane Library (1993~2015.10), PubMed (1970~2015.10), CBM (1978~2015.10), CNKI (1996~2015.10), Wanfang Data (1999~2015.10), VIP database (1996~2015.10) and Google scholar were searched by a computer, and relevant journals were manually searched. The full-text references were obtained. Search terms: “Non-small cell lung cancer”, “NSCLC”, “gefitinib”, “irressa”, “docetaxel”, “randomized controlled trial”.

Quality assessment and data extraction

The reference quality was evaluated according to the quality standards of RCT in the Cochrane Handbook for Systematic Reviews of Interventions version 5.0 [16]. The main evaluation items were as follows: whether the random method was correct, whether the blinding method was used, whether the allocation concealment was used, whether there was loss of follow-up or withdrawal, if had, whether intention to treat analysis was used. Literature screening, literature quality evaluation and data extraction were independently performed by two researchers. Cross check was performed, and disagreement was resolved by discussion with a third researcher. The researcher firstly read the titles and abstracts of all the obtained references and excluded the trials that obviously did not meet the inclusion criteria. Then, the full texts of those references which might meet the inclusion criteria were read to determine if they actually met the inclusion criteria. The data was extracted using a self-made data extraction table.

Statistical analysis

Quantitative and qualitative analysis were performed for the collected data. The software RevMan 5.2 of the Cochrane Collaboration was used for meta-analysis. The clinical and methodological heterogeneities were first analyzed for the included researches, and the statistical heterogeneity was checked by $\chi^2$ test and $I^2$ test. When $P>0.1$ and $I^2<50\%$, it indicated that there was no statistical heterogeneity between the researches, and thus the fixed effects model was used for the meta-analysis. When $P\leq0.1$ and $I^2\geq50\%$, it indicated that there was statistical heterogeneity between the researches, and thus the subgroup analysis (based on the possible factors with heterogeneity) or sensitivity analysis was used. If there was still heterogeneity, for the data that could be combined from the aspect of clinical significance, the meta-analysis was performed using random effects model, and
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Results of meta-analysis

1-year survival rate: There were 8 researches reported 1-year survival rate, including a total of 2519 patients. The result of the heterogeneity test was $P=0.73$ and $I^2=0\%$, and thus the fixed effects model was used. The meta-analysis result showed that RR=0.91, 95% CI (0.83, 1.01) and $P=0.07$, and the difference had no statistical significance (Figure 2). The results indicated that the 1-year survival rate of gefitinib-treated NSCLC patients was not significantly different from that of the patients treated with docetaxel.

Overall response rate: There were 10 researches reported ORR, including 2416 patients. The result of the heterogeneity test was $P=0.11$ and $I^2=38\%$, and thus the fixed effects model was used. Meta-analysis result showed that RR=1.40, 95% CI (1.18, 1.65), $P<0.0001$, and the difference was statistically significant (Figure 3). The results indicated that the ORR for gefitinib-treated NSCLC patients were obviously better than that of the patients treated with docetaxel.

Disease control rate: There were 9 researches reported DCR, including 1004 patients. The result of the heterogeneity test was $P=0.89$ and $I^2=0\%$, and thus the fixed effects model was used. Meta-analysis result showed that RR=1.12, 95% CI (1.06, 1.19), $P=0.001$, and the difference had no statistical significance (Figure 4). The results indicated that the DCR of gefitinib for the treatment of NSCLC were not obviously better than that of the patients treated with docetaxel.

TOI improvement rate: There were 7 researches reported TOI improvement rate, including 2243 patients. The result of the heterogeneity test was $P=0.08$ and $I^2=47\%$, and thus the fixed effects model was used. Meta-analysis result showed that RR=1.89, 95% CI (1.56, 2.29), $P<0.00001$, and the difference had statistical significance (Figure 5). The results indicated that the TOI improvement of gefitinib-treated NSCLC patients was obviously better than that of the patients treated with docetaxel. Therefore, heterogeneous sources were analyzed. After excluding the studies by Sekine...
Table 1. The features of the included studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Published language</th>
<th>Ethnicity</th>
<th>Study location</th>
<th>Intervention</th>
<th>Participant Age median (range)</th>
<th>Disease stage</th>
<th>Quality evaluation</th>
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<td>Multicenter</td>
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<td>Asians</td>
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<td>Gefitinib</td>
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<tr>
<td>Zhang Yi 2009 [24]</td>
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<td>Asians</td>
<td>China</td>
<td>Gefitinib</td>
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<td>Dae Ho Lee 2010 [25]</td>
<td>English</td>
<td>Asians</td>
<td>Korea</td>
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<td>82 57 - - - -</td>
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<td>40 66 - - - -</td>
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Table 2. The methodological quality of the included studies

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<th>Incompleteness of data</th>
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Figure 2. The meta-analysis of the 1-year survival rates of gefitinib vs. docetaxel for the treatment of NSCLC. It showed that RR=0.91, 95% CI (0.83, 1.01) and \( P = 0.07 \), and the difference had no statistical significance.

Figure 3. The meta-analysis of the overall response rates of gefitinib vs. docetaxel for the treatment of NSCLC. It showed that RR=1.40, 95% CI (1.18, 1.65), \( P < 0.0001 \), and the difference was statistically significant.

Figure 4. The meta-analysis of the disease control rates of gefitinib vs. docetaxel for the treatment of NSCLC. It showed that RR=1.12, 95% CI (0.96, 1.29), \( P = 0.15 \), and the difference had no statistical significance.
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Figure 5. The meta-analysis of the TOI improvement rates of gefitinib vs. docetaxel for the treatment of NSCLC. It showed that RR=1.89, 95% CI (1.56, 2.29), P<0.00001, and the difference had statistical significance.

Figure 6. The meta-analysis of the incidence of neutropenia of gefitinib vs. docetaxel for the treatment of NSCLC. It showed that RR=0.16, 95% CI (0.07, 0.36), P<0.00001, and the difference had statistical significance.

[22] and Maruyama [19], the heterogeneity reduced to 10%. The reason may be that the research objects in these two references were mainly Japanese population. After excluding these two researches, the combined RR analytical result was 1.65 [95% CI (1.33, 2.04), P=0.0001], which had no influence on the final conclusion.

Incidence of neutropenia: There were 6 researches reported the incidence of neutropenia, including 2332 patients. The result of the heterogeneity test was P<0.0001 and I²=82%, and thus the random effects model was used. Meta-analysis result showed that RR=0.16, 95% CI (0.07, 0.36), P<0.00001, and the difference had statistical significance (Figure 6). The results indicated that the incidence of neutropenia of gefitinib-treated NSCLC patients was obviously lower than that of the patients treated with docetaxel. Due to the large heterogeneity of the included studies, the sources of heterogeneity were analyzed. After excluding the study by Kim [18], the heterogeneity decreased to 31%. The reason may be that the objects in all the other 5 references were Asian population, but the objects in Kim’s study [18] mixed many races. After excluding this study, the combined RR analytical result was 0.06 [95% CI (0.02, 0.17), P<0.00001], which had no influence on the final conclusion.

Discussion

Chemotherapy is mainly used for the treatment of advanced NSCLC. Currently used third-generation first-line chemotherapy for the treatment of advanced NSCLC has an effective rate of 35%, 1-year survival rate of 35% and 2-year survival rate of 20% [31]. For the second-line chemotherapy after the failure of the first-line chemotherapy, the National Comprehensive Cancer Network (NCCN) guideline recommends docetaxel and pemet-
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rexed, and pemetrexed is only recommended for the non-squamous cell carcinoma patients [32]. Docetaxel is a new anti-microtubule drug, whose microtubule stabilizing effect is twice greater than that of taxol. It is a cell cycle specific drug and can block the cell in M phase. It also can interfere with cell mitosis, and thus kill tumor cells [33]. However, drug-resistant cell lines increased after the failure of first-line chemotherapy, its efficacy is limited. References reported that the tumor objective response rate of docetaxel as second-line chemotherapy was only 5.5%–6.7%, the median tumor progression free time was only 8.5–10.6 weeks, the median survival time was only 5.7–7.5 months [34]. In addition, docetaxel chemotherapy requires higher physical state for the patients. Many patients have a physical score >2 after the failure of the first-line chemotherapy, who cannot receive further chemotherapy [35]. In the treatment of lung cancer, epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) is a research hotpot in recent years. Gefitinib, erlotinib, vandetanib and a large number of other targeted drugs show good clinical efficacy and low toxic and side effects [36]. The results of this study showed that gefitinib could obviously improve the overall response rate and TOI improvement rate, and reduce the hematological toxicity.

The RCTs included in this study had some defects in the research design, mainly in the following aspects: 1) only 8 studies described detailed randomized method, while the rest of the studies did not make full randomization of the study objects, which might result in selective bias; 2) insufficient attention to allocation concealment, which might exaggerate the treatment effect; 3) the use of blind method was too low, which might produce implementation bias and measurement bias; 4) the reasons for the loss of the case and follow-up and withdrawal were not described, which might affect the evaluation of therapeutic effects; 5) all the included studies did not explain the calculation of sample size, which would reduce the test efficiency; 6) the included studies did not describe the baseline in detail, which made it hard to judge the balance between groups. In addition, all studies were lack of economic evaluation. Therefore, further researches are needed to guide the clinical application of gefitinib.

In conclusion, gefitinib has some advantages in the treatment of NSCLC, and can be used as conventional drugs for NSCLC treatment. However, because the application of gefitinib is affected by economic conditions and the quality of the included literature is uneven, the clinical application of gefitinib needs supports from more high quality clinical studies and economic evaluations.

Acknowledgements

We would like to thank Mr. Changfu Li from The Cancer Hospital Affiliated to Harbin Medical University for his help in this study. We would like to thank Mr. Wuyong Zhong from Chongqing Cancer Hospital for his help in this study.

Disclosure of conflict of interest

None.

Address correspondence to: Aihong Zhang, Department of Pharmacy, The Cancer Hospital Affiliated to Harbin Medical University, No. 150 Heping Road, Nangang District, Harbin 1500086, P. R. China. Tel: 0451-86298568; Fax: 0451-86298568; E-mail: cnq333@163.com

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