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Original Article

Chemotherapy plus Vandetanib or Chemotherapy Alone in Advanced Non-small Cell Lung Cancer: A Meta-analysis of Four Randomised Controlled Trials

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Abstract

Aims: Most patients with advanced non-small cell lung cancer (NSCLC) require systemic chemotherapy. Vandetanib, targeting epidermal growth factor receptor and vascular endothelial growth factor receptor signalling in NSCLC, has recently been evaluated in combination chemotherapy in advanced NSCLC. However, the advantage of chemotherapy plus vandetanib over chemotherapy alone in advanced NSCLC remains largely unknown. A meta-analysis of randomised controlled trials was carried out to compare the efficacy and toxicity of chemotherapy plus vandetanib with chemotherapy alone in advanced NSCLC.

Materials and methods: The PubMed database, American Society of Clinical Oncology, European Society for Medical Oncology and the Cochrane Library and references of published trials were searched. Two reviewers independently assessed the quality of the trials. Data were extracted and the overall response rate, pooled progression-free survival, overall survival with 95% confidence intervals and main toxicity were analysed.

Results: Four randomised controlled trials involving 2160 patients with advanced NSCLC were ultimately analysed. Compared with chemotherapy alone, chemotherapy plus vandetanib significantly increased the overall response rate (relative risk = 1.96, 95% confidence interval = 1.53––2.52) and progression-free survival (hazard ratio = 0.79, 95% confidence interval = 0.71–0.87), but there was no significant difference in overall survival (hazard ratio = 0.91, 95% confidence interval = 0.79–1.03). Patients who received chemotherapy plus vandetanib had more rash, diarrhoea, hypertension and QTc prolongation (odds ratio = 2.32, 95% confidence interval = 1.93–2.79; odds ratio = 1.64, 95% confidence interval = 1.37–1.97; odds ratio = 4.08, 95% confidence interval = 2.51–6.01, odds ratio = 17.77, 95% confidence interval = 3.54–61.66, respectively), and less nausea and vomiting (odds ratio = 0.70, 95% confidence interval = 0.58–0.85; odds ratio = 0.69, 95% confidence interval = 0.55–0.86, respectively). The incidences of haemorrhage, fatigue and cough were comparable between the two groups.

Conclusions: Although similar in overall survival, chemotherapy plus vandetanib showed particular advantages over chemotherapy alone in terms of progression-free survival and overall response rate. The toxicity was comparable between the two groups. Therefore, chemotherapy plus vandetanib might be a safe and valid therapeutic option for advanced NSCLC patients.

Key words: Meta-analysis; non-small cell lung cancer; overall response rate; overall survival; progression-free survival; randomised controlled trials; vandetanib

Introduction

Lung cancer, the leading cause of cancer-related death for men and women worldwide in 2010, is responsible for more deaths than a combination of those caused by colorectal cancer, breast cancer and prostate cancer [1]. About 85% of lung cancer cases are categorised as non-small cell lung cancer (NSCLC) and most are presented as advanced stage at the first visit [1, 2]. Platinum-based doublets are the standard first-line therapy for patients with advanced NSCLC [3], with about one-third of patients obtaining an objective response with first-line chemotherapy and another 20–30% achieving temporary disease stabilisation. However, all patients inevitably experience disease progression. Docetaxel [4,5] and pemetrexed [6] have been approved as second-line chemotherapy for advanced NSCLC, but have not been shown to be better in this setting. Whatever first-line or second-line chemotherapy, an efficacy plateau may be reached when it is used alone. The prognosis for lung cancer patients is generally poor, with an overall 5 year survival rate of about 10–15%, and it has shown little improvement in recent decades [2,7].

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The strategy for improving efficacy and alleviating symptom burden, without increasing toxicity, is to combine chemotherapeutics with drugs thats electively target signalling pathways associated with lung cancer progression. Vascular endothelial growth factor receptor (VEGFR)-dependent tumour angiogenesis and epidermal growth factor receptor (EGFR)-dependent tumour cell proliferation are clinically validated therapeutic targets in NSCLC [8–11]. Moreover, EGFR is known to regulate the production of VEGF and other proangiogenic factors [12], and increased VEGF expression has been associated with resistance to EGFR inhibition in a human tumour xenograft model of NSCLC [13]. Bevacizumab, an anti-VEGF monoclonal antibody, is currently the only approved anti-angiogenic agent for patients with NSCLC [8] and EGFR inhibitors, such as gefitinib and erlotinib, have shown single-agent activity in advanced NSCLC [9,10]. Dual targeting of VEGFR and EGFR signalling in NSCLC is therefore a rational therapeutic approach [14].

Vandetanib (AstraZeneca, Macclesfield, UK) is a once-daily, oral anticancer agent that inhibits VEGFR, EGFR and rearranged during transfection (RET)-dependent signalling [15,16].Phase I evaluation in patients with solid tumours showed that vandetanib was generally well tolerated at $\leq$300 mg/day [17].

Vandetanib in combination with first- or second-line chemotherapyin advanced NSCLC patients has been evaluated, but the several randomised controlled trial (RCT) results of its efficacy and safety are inconsistent [18–21]. The objectives of this meta-analysis were to compare the efficacy and toxicity of chemotherapy plus vandetanib with chemotherapy alone in advanced NSCLC patients.

Materials and Methods

Search Strategy

In September 2011, an electronic search of the Medline (PubMed, www.ncbi.nlm.nih.gov/PubMed), American Society of Clinical Oncology (www.asco.org), European Society for Medical Oncology (www.esmo.org) and the Cochrane Library was carried out. The following key words were used: 'non-small cell lung cancer', 'vandetanib'. The published languages and years were not limited. In addition to computer browsing, review articles and original papers were scanned in the reference section to look for missing trials. Furthermore, abstracts presented at major meetings (American Society of Clinical Oncology, European Society for Medical Oncology, European Cancer Organisation (ECCO), and World Congress on Lung Cancer (WCLC)) were also searched. We also reviewed the Cochrane Library for relevant articles (http://www.thecochranelibrary.com/view/0/index.html).

Selection of Trials

The meta-analysis was conducted in order to ascertain the significant difference of primary and secondary outcomes in the patients with advanced NSCLC. Treatment with chemotherapy plus vandetanib was considered as the experimental arm and chemotherapy alone as the standard arm. The primary outcome for the magnitude of benefit analysis was progression-free survival (PFS). Secondary end points included the overall response rate (ORR), overall survival and toxic effects according to the World Health Organization scoring system or the National Cancer Institute–Common Toxicity Criteria for Adverse Events, respectively. The RCTs were eligible if chemotherapy plus vandetanib was compared with chemotherapy alone in the first- or second-line treatment of advanced NSCLC. Patients should be pathologically confirmed NSCLC and in clinical IIIB–IV stage; randomised phase II and III trials were included. Trials were excluded if they did not meet the above inclusion criteria.

Quality Assessment

An open assessment of the trials was carried out using the methods reported by Jadad and colleagues [22], which assessed the trials according to the following three questions: (1) whether it reported an appropriate randomisation method (0–2 scores); (2) whether it reported an appropriate blinding method (0–2 scores); (3) whether it reported withdrawals and dropouts (0–1 score).

Data Abstraction

All the data were independently abstracted by two investigators (PZ, DY) according to the inclusion criteria listed above. Disagreements were resolved by discussion with an independent expert (YX). The following information was sought from each paper, although some papers did not contain all of them: trial's name, first author, year of publication, journal, quality scores according to Jadad and colleagues' methods [22], ethnicity, number of patients in both groups, age, gender, performance status 0–2, smoking history, histology, stage of disease, hazard ratios for PFS and their 95% confidence intervals, hazard ratios for overall survival and their 95% confidence intervals, number of patients who acquired an overall response assessed with Response Evaluation Criteria In Solid Tumors (RECIST), data for toxicities such as hypertension, vomiting, diarrhoea, fatigue and rash, etc.

Statistical Analysis

Hazard ratios for PFS and overall survival, the relative risk for an overall response to treatment and odds ratios for different types of toxicity were calculated. Analyses were carried out in intention-to-treat for PFS, overall survival, ORR and toxicities. A statistical test with a P-value less than 0.05 was considered as significant. A hazard ratio > 1 reflects more progression or deaths in chemotherapy with the vandetanib group, a relative risk > 1 reflects more overall response in chemotherapy with the vandetanib group and an odds ratio > 1 indicates more toxicities in chemotherapy with the vandetanib group. To investigate statistical heterogeneity among different trials, the standard χ^2 Q-test was applied (meaningful differences between studies indicated by $P < 0.10$). The results were generated using a fixed-effect