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Erlotinib in combination with bevacizumab has potential benefit in non-small cell lung cancer: A systematic review and meta-analysis of randomized clinical trials

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ABSTRACT

Objectives: A role for erlotinib and bevacizumab as single agents has been established in the treatment of non-small cell lung cancer (NSCLC). However, the efficacy and safety of erlotinib in combination with bevacizumab compared with single agents remain unclear. This meta-analysis aimed to investigate the status of this combined strategy in NSCLC.

Materials and methods: We systematically searched relevant databases for randomized controlled trials (RCTs) on the use of erlotinib plus bevacizumab in NSCLC. The main outcomes analysis reported overall survival (OS), progression-free survival (PFS), objective response rate (ORR), and adverse effects. Random-effects models were used to estimate pooled hazard ratio and relative risk.

Results: Ten studies with a total of 2802 participants were eligible for meta-analysis, the results of which suggested erlotinib with bevacizumab failed to significantly enhance either OS (95% CI: 0.87–1.12; $P = 0.825$) or ORR (95% CI: 0.69–1.67; $P = 0.758$). Though PFS was modestly improved, there was no statistical significance (5.55 months vs. 4.67 months, 95% CI: 0.63–1.15; $P = 0.297$). Incidence of rash or diarrhea was higher in the combination group than in the single-agent group. Subgroup analysis showed encouraging OS (95% CI: 0.29–0.69; $P < 0.001$) in epidermal growth factor receptor (EGFR)-mutant patients treated with combination therapy, no such benefits were found in groups restricting on KRAS status.

Conclusion: Erlotinib plus bevacizumab enhances OS for EGFR-mutant patients, with rash and diarrhea common but acceptable adverse effects. Combination treatment can be recommended as the preferable option for EGFR-mutant patients. Further large-scale, well-designed RCTs are required to confirm our validation.

1. Introduction

In recent decades, lung cancer has remained the leading global cause of cancer-related mortality with an evaluation of 1.6 million deaths each year. The most frequently occurring type, non-small cell lung cancer (NSCLC), accounts for 80%–85% of cases and has a 5-year survival rate of less than 20% [1,2]. Tobacco smoking is the principal etiology for lung cancer, accounting for 80% of cases in the United States and other countries where smoking is common. With vigorous efforts from cancer agencies, committed organizations, and the oncology community, the incidence of smoking has, fortunately, shown a downward trend. Surgery, radiotherapy, and chemotherapy are regarded as standard treatments for NSCLC patients; however, their efficacy and adverse effects (AEs) are not satisfactory. Bevacizumab (Avastin), a humanized monoclonal antibody directed against vascular endothelial growth factor (VEGF), shows promise in treating a number of types of cancer [3]. Approved by the US Food and Drug Administration in 2004, bevacizumab has displayed encouraging activity, enhancing patients' overall survival (OS) and progression-free survival (PFS) [4]. Erlotinib, an epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) also demonstrates notable efficacy in NSCLC [5]. Erlotinib was approved by the Food and Drug Administration for use in the circumstance of a lack of response to more than one previous chemotherapy regimen, and its use is also suggested for patients harboring common EGFR mutations such as E746–A750 deletion in exon 19 and L858R missense in exon 21 [6]. The amplification of exons 2 and

Abbreviations: NSCLC, non-small cell lung cancer; RCTs, randomized controlled trials; OS, overall survival; PFS, progression free survival; ORR, objective response rate; AEs, adverse effects; HR, hazard ratio; RR, relative risk; CI, confidence intervals; FDA, Food and Drug Administration; VEGF, against vascular endothelial growth factor; EGFR-TKI, epidermal growth factor receptor tyrosine kinase inhibitor; KRAS, Kirsten rat sarcoma; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement; PROSPERO, International Prospective Register of Systematic Reviews; ECOG, Eastern Cooperative Oncology Group

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3 of the Kirsten rat sarcoma (KRAS) gene has also drawn attention; some studies have convincingly and consistently demonstrated the superiority of erlotinib over standard platinum first-line chemotherapy in EGFR-mutated patients [7–10].

Bevacizumab in combination with platinum-based chemotherapy and erlotinib in EGFR-sensitive patients are both regarded as first-line treatments for NSCLC. Although there is a general impression that erlotinib plus bevacizumab has an important therapeutic value in NSCLC, the role of erlotinib in combination with bevacizumab, compared with monotherapy, has remained unclear. Phase I/II studies of treatment with erlotinib in combination with bevacizumab in non-squamous NSCLC patients have exhibited reassuring OS and reasonably prolonged PFS [11,12]. However, previous studies lacked adequately powered statistics, consecutive endpoints, and subgroup analyses that involved analysis of selection, reporting and publication bias. Thus, the overall quantitative analysis of erlotinib in combination with bevacizumab in the treatment of NSCLC is not yet sufficient, and implementation in clinical practice is suboptimal. Additionally, most of the studies failed to report the mutation status of included patients under the targeted therapy. Thus, to contribute to current and convincing evidence for clinical management, we conducted a timely systematic review and meta-analysis to determine whether this combined strategy was more effective than monotherapy in NSCLC. A secondary objective was to investigate whether efficacy differed between wild-and mutant-type EGFR and KRAS status.

2. Material and methods

This meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [13] (**Table S1**). The study was also registered in the PROSPERO international register of systematic reviews (CRD 42017069667).

2.1. Search strategy

The PubMed, Embase, and Cochrane Central Trials databases were rigorously reviewed for randomized controlled trial (RCT) reports published between 1 January 2000 and 30 August 2017 focusing on the combination of erlotinib and bevacizumab in NSCLC, without language restrictions. The combined text and medical subject heading (MeSH) terms used were: “Carcinoma, Non-Small-Cell Lung” and “Erlotinib Hydrochloride” and “Bevacizumab”. The complete search terms for PubMed included: (Carcinoma, Non-Small-Cell Lung [MeSH terms] OR Carcinoma, Non Small Cell Lung [Text Word]) AND (Erlotinib Hydrochloride [MeSH term] OR Hydrochloride, Erlotinib [Text Word]) AND (Bevacizumab [MeSH term] OR Avastin [text]). We also manually searched the reference lists of the retrieved literature for further eligible articles.

2.2. Selection criteria

Studies that met the following criteria were included [14]:

(1) Population: adult patients with histologically or cytologically confirmed NSCLC with Eastern Cooperative Oncology Group performance status scores of 2 or lower. There were no special restrictions on sex, race, nationality, clinical tumor stage, histology, smoking and alcohol history, or EGFR or KRAS status. Essential pretreatment was also allowed.
(2) Intervention: erlotinib plus bevacizumab.
(3) Comparison: erlotinib or bevacizumab as a single agent.
(4) Outcome: OS, PFS, objective response rate (ORR), and AEs.
(5) Study design: high-quality RCTs.

Only the most novel and complete reports were included, to avoid duplicate information; reviews without original data as well as animal experimental studies and meta-analyses were excluded. There was no significant difference in pretreatments or other irrelevant elements.

2.3. Data extraction and quality assessments

We recorded the available reported hazard ratio (HR) and relative risk (RR) for the outcome of combined therapy compared with monotherapy. Corresponding data were also extracted by 2 independent investigators (W X Zhang and D L Yu) from each study as follows: the first author, year of publication, region, number and basic characteristics of participants, tumor histology and clinical stage, smoking history, EGFR status, intervention and outcome data, and study phase and design. The acquired information and original data were entered into standardized tables. Discrepancies were resolved by discussion with a third investigator (Y P Wei). The Cochrane Risk of Bias Tool was adopted to assess risk of bias for each RCT. Seven items were used to evaluate heterogeneity in each trial: randomization sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases. The quality of each study was categorized as high, low, or unclear [15].

2.4. Outcomes assessed

OS, PFS, ORR, and AEs were specifically defined as the main outcomes, pinpointing the efficacy and safety of the combination treatment. Based on a priori hypotheses to explain potential heterogeneity and variability in the direction of and prominence of effect between the various studies, we conducted a post-subgroup analysis. The efficacy of erlotinib plus bevacizumab in different EGFR and KRAS status was also specifically identified by subgroup analysis.

2.5. Statistical analysis

For the included studies, we calculated HR with 95% confidence intervals (CIs) for time-to-event variables, including OS and PFS. RR with 95% CI was calculated for binary variables, including ORR and incidence of AEs. Some studies reported relevant HR information for our outcomes directly. In other studies Kaplan–Meier curves were provided rather than HR data; in these conditions we extracted and estimated HR and 95% CI from the Kaplan–Meier curves according to Tierney et al. [16]. Heterogeneity across studies was evaluated using Cochran Q chi-square test and I^2 statistic [17]. An $I^2 > 50\%$ or a P value for Q test < 0.1 was regarded as indicating significant heterogeneity [18]. We used random-effects models because these assumptions accounted for the presence of within-study and between-study variability. We also conducted a sensitivity analysis to investigate the influence of a single study on the overall estimate size by omitting one study in turn if there was significant heterogeneity.

Potential publication bias was assessed using Begg’s rank correlation [19] and Egger’s linear regression [20] tests. All analyses were performed using Stata (version 12.0) and Revman (version 5.3); two-sided $P < 0.05$ was considered statistically significant except where otherwise specified.

3. Results

3.1. Search results

A total of 754 potentially eligible studies were identified by searching the relevant databases using the keywords. Forty-eight records were excluded as duplications and the remaining 706 studies were reviewed for title and abstract. We excluded 683 studies for being reviews; animal experiments; meta-analyses; or irrelevant to the topic. The remaining 23 studies underwent detailed full-text evaluation and