Lung Cancer 85 (2014) 339–345

Contents lists available at ScienceDirect

Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan

Review

EGFR mutations and clinical outcomes of chemotherapy for advanced non-small cell lung cancer: A meta-analysis

Qiong Zhang[a], Hong-Hai Dai[a], Hong-Yun Dong[b,c], Cheng-Tao Sun[a], Zhe Yang[a,*,1], Jun-Qing Han[a,*,1]

[a] Tumor Research and Therapy Center, Provincial Hospital Affiliated to Shandong University, 324 Jingwu Weiqi Road, Jinan, Shandong 250021, PR China
[b] School of Public Health, Shandong University, 44 Wenhuaxi Road, Jinan, Shandong 250012, PR China
[c] Wanhua Chemical Group Co., Ltd., 7 South Xingfu Road, Yantai, Shandong 264002, PR China

ARTICLE INFO

Article history:
Received 11 October 2013
Received in revised form 20 April 2014
Accepted 13 June 2014

Keywords:
Non-small cell lung cancer
EGFR
Mutation status
Chemotherapy
Response rate
Meta-analysis

ABSTRACT

Background: This meta-analysis was performed to assess whether epidermal growth factor receptor (EGFR) mutation status was associated with objective response rate (ORR), progression-free survival (PFS), and overall survival (OS) in patients with advanced non-small cell lung cancer (NSCLC) treated with chemotherapy.
Method: We systematically identified eligible articles investigating the effects of chemotherapy in patients with NSCLC stratified by EGFR mutation status. The summary risk ratio (RR) for ORR and hazard ratios (HRs) for both PFS and OS were calculated using the inverse variance formula of meta-analysis.
Results: Identification for the current meta-analysis: 5 prospective studies (n = 875) and 18 retrospective studies (n = 1934) for ORR; 2 prospective studies (n = 434) and 10 retrospective studies (n = 947) for PFS; 2 prospective studies (n = 438) and 7 retrospective studies (n = 711) for OS. The ORR was significantly higher in patients with EGFR mutations in prospective studies (RR = 1.42; 95% confidence interval [CI], 1.16–1.74; P = 0.001), but not in retrospective studies (RR = 1.12; 95% CI, 0.96–1.32; P = 0.146). There was no obvious association between EGFR mutations and PFS both in prospective (HR = 0.84; 95% CI: 0.65–1.09; P = 0.197) and retrospective (HR = 1.02; 95% CI: 0.87–1.18; P = 0.838) studies. Association between EGFR mutations and OS was also not seen in prospective studies (HR = 0.74; 95% CI: 0.27–2.05; P = 0.566), but was seen in retrospective studies (HR = 0.48; 95% CI: 0.33–0.72; P < 0.001; I^2 = 75.9%; P < 0.001) with significant heterogeneity.
Conclusion: EGFR mutations in advanced NSCLC may be associated with higher ORRs to chemotherapy, but may have nothing to do with PFS and OS. Further prospective studies are required to identify the influence of EGFR mutations on chemotherapy effects in advanced NSCLC.

1. Introduction

The development and utilization of epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) was a great advancement in the treatment of specific cases of advanced non-small cell lung cancer (NSCLC). EGFR mutations have been demonstrated to predict good efficacy of EGFR-TKIs in NSCLC [1–4]. Consequently, it is important to confirm the EGFR genotype of patients with NSCLC to determine whether EGFR-TKI therapy would be appropriate. Although EGFR-TKIs play a critical role in the treatment of advanced NSCLC, chemotherapy with conventional anticancer agents is still the gold-standard approach for patients with unresectable, locally advanced, or metastatic NSCLC. Nevertheless, the association between EGFR genotype and the effects of chemotherapy remains uncertain.

With the emphasis on biomarkers in the treatment of NSCLC, many studies have been conducted to investigate the biomarkers predicting patient response to specific chemotherapy regimens [5–7]. In the Iressa Pan-Asia Survival Study (IPASS) [4], Asian patients with EGFR mutations had a significantly higher response rate (47.3% versus 23.5%) than patients without EGFR mutations when they received paclitaxel plus carboplatin as first-line therapy. Similar results were observed in 2 other studies [8,9].

However, 2 preclinical experiments demonstrated that lung cancer cells or tumors with EGFR mutations may tend to markedly

* Corresponding authors at: Tumor Research and Therapy Center, Provincial Hospital Affiliated to Shandong University, 324 Jingwu Weiqi Road, Jinan, Shandong 250021, PR China. Tel.: +86 531 6877 6100; fax: +86 531 87068707.
E-mail addresses: sdslyyyz@sina.com (Z. Yang), hanjq1960@126.com (J.-Q. Han).
[1] These two corresponding authors contributed equally to this work.

http://dx.doi.org/10.1016/j.lungcan.2014.06.011
0169-5002/

resist chemotherapeutic agents [10,11]. Consistent with this, several clinical studies have suggested patients with mutated EGFR have poorer responses to chemotherapy than patients with wild-type EGFR [12–14]. Furthermore, different studies using the same methods to detect EGFR mutation status and the same chemotherapeutic agents have yielded contradictory results [9,14]. Because of these inconsistent results, we conducted a meta-analysis to evaluate the role of EGFR mutation status in predicting the efficacy, progression-free survival (PFS), and overall survival (OS) of chemotherapy in patients with advanced NSCLC. In this article, the word "chemotherapy" represents chemotherapy with conventional anticancer agents.

2. Materials and methods

2.1. Literature search strategy

We performed computerized searches of the PubMed database, the EMBASE database and the Cochrane library (Issue 6, 2013) to identify all published articles reporting on chemotherapy for advanced NSCLC with known EGFR mutation status using the following key words: non-small cell lung cancer, NSCLC, lung cancer, chemotherapy, and epidermal growth factor receptor. The search was performed on July16, 2013. The published languages were not limited. The references of all reviewed articles were also screened for additional studies.

2.2. Selection criteria

Eligible studies had to meet the following criteria:(1) patients with advanced or recurrent NSCLC; (2) detected EGFR gene mutation status in primary lung cancer tissue, metastatic tissue or sera DNA; (3) received chemotherapy; (4) reported data of response rate, the hazard ratios (HRs) with the corresponding 95% confidence intervals (CIs) comparing OS, PFS or time-to-progression (TTP) stratified by EGFR mutation status; and (5) the number of patients in the EGFR mutation or wild-type group was not less than 5. Studies examining chemotherapy in combination with any other agents such as EGFR-TKIs, any investigational drug or radiotherapy were excluded.

2.3. Quality assessment

Two investigators (QZ, HYD) independently assessed the quality of studies using the Newcastle Ottawa Quality Assessment Scale for cohort studies [15,16]. Discrepancies were resolved by consensus. This scale is composed of eight items which assess patient selection, study comparability and outcome. The scale was recommended by the Cochrane Non-Randomized Studies Methods Working Group [17].

2.4. Data extraction

Data from each study were extracted independently by 2 investigators, using a standardized data extraction form. Disagreements between the 2 investigators were resolved by consensus. The following information was abstracted from each publication: authors, publication date, country, sample size, study type, characteristics of the patients, data about EGFR mutations, test methods, numbers of patients in the EGFR mutation and wild-type groups, chemotherapy information, objective response rates (ORRs), and HRs and 95%CIs for PFS (or TTP) and OS.

2.5. Statistical methods

The risk ratio (RR) was calculated for ORRs, and the HR was calculated for PFS and OS. In studies without HRs, Kaplan–Meier plots were used to calculate the HRs based on the methods presented by Tierney [18].

STATA SE 12.0 package (StataCorp, College Station, TX, USA) was used for statistical analyses. The fixed-effects model (inverse variance formula) was initially used. If P (for I^2) < 0.05, indicating significant heterogeneity among studies, then the random-effects model (I–V heterogeneity formula) was used. Two-tailed P values were used for all comparisons, and statistical significance was defined as $P < 0.05$. The possibility of publication bias was investigated by inspecting funnel plots and was statistically analyzed using Begg's test.

We planned additional sensitivity analyses to further detect and evaluate clinical heterogeneity. Most of the eligible studies used first-line chemotherapy with platinum-based double-agent regimens (17/23), with the second agent varying between studies (Supplementary Table 1). Consequently, it was difficult to perform subgroup analyses according to the therapeutic regimen. There also was not enough data about pathological types and sex to perform separate analyses of these subgroups. Finally, subgroup analyses were conducted to assess the effects of ethnicity (Asian, Caucasian, or mixed), therapy line (first-line, second-line, and mixed-line), and test methods of EGFR genotype (scorpions amplification refractory mutation system [Scorpions ARMS] or direct DNA sequencing or denaturing high performance liquid chromatography [DHPLC]). Therefore the categories used to make subgroup analysis were not pre-specified. We performed sensitivity analysis for studies providing HRs and for some categories without sufficient studies for subgroup analysis in the additional analysis of PFS and OS. Studies conducted in Korea, China, Japan and other Asian countries were classified as "Asian" and studies conducted in Spain, American, England, and other European countries were classified as "Caucasian."

3. Results

3.1. Eligible studies

The search yielded 1639 references. Ultimately, 23 studies with 2809 patients were used for the meta-analysis. Fig. 1 shows the reasons for excluding the other 1616 articles. A total of 1069 out of 2809 patients harbored EGFR mutations. Five prospective studies ($n = 875$) and 18 retrospective studies with 20 groups of data ($n = 1934$) were included in the pooled analysis of ORR, 2 prospective studies ($n = 434$) and 10 retrospective studies with 12 groups of data ($n = 947$) were included in the analysis of PFS, and 2 prospective studies ($n = 438$) and 7 retrospective studies ($n = 711$) were included in the analysis of OS. The characteristics of the eligible studies are summarized in Table 1.

The Newcastle-Ottawa Scale was used to perform quality assessment on all 23 studies. This scale has been used in other non-randomized studies [19]. Studies that fulfill 5 or more of the 8 criteria (more than 5 stars) were defined as high-quality studies. All studies included in this meta-analysis scored highly (not shown).

Two articles [20,21] both had first-line and second-line chemotherapy information; therefore, appropriate data were included separately in the analysis from these studies. Ultimately, 15 studies containing 17 groups of data were from Asians, 6 studies were from Caucasians, and 2 studies were considered to be "mixed", containing both Asian and Caucasian patients. Seventeen