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Is there evidence for different effects among EGFR-TKIs? Systematic review and meta-analysis of EGFR tyrosine kinase inhibitors (TKIs) *versus* chemotherapy as first-line treatment for patients harboring EGFR mutations

Eva Regina Haspinger[a], Francesco Agustoni[a], Valter Torri[b], Francesco Gelsomino[a], Marco Platania[a], Nicoletta Zilembo[a], Rosaria Gallucci[a], Marina Chiara Garassino[a,*], Michela Cinquini[b]

[a] *Medical Oncology, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy*
[b] *Fondazione IRCCS Istituto di Ricerche Farmacologiche Mario Negri, Milan, Italy*

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Contents

Abstract

Three EGFR tyrosine kinase inhibitors have been compared to standard chemotherapy as up-front treatment in patients with advanced EGFR-positive NSCLC. We performed a systematic review and meta-analysis using indirect comparisons to estimate the risk/benefit associated with each drug. EGFR-TKIs fared better than chemotherapy in terms of PFS. The relative probability of overall response was gefitinib *versus*

* Corresponding author. Tel.: +39 02 2390 3813; fax: +39 02 2390 2149.
E-mail address: marina.garassino@istitutotumori.mi.it (M.C. Garassino).

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erlotinib 0.96 (95% CI 0.69–1.34), gefitinib *versus* afatinib 0.91 (95% CI 0.67–1.23), erlotinib *versus* afatinib 0.94 (95% CI 0.65–1.35). Indirect comparisons for safety showed the RR for diarrhea gefitinib *versus* erlotinib 0.80 (95% CI 0.63–1.01), gefitinib *versus* afatinib 0.29 (95% CI 0.20–0.41), erlotinib *versus* afatinib 0.36 (95% CI 0.25–0.54); for rash gefitinib *versus* erlotinib 1.00 (95% CI 0.82–1.22), gefitinib *versus* afatinib 0.41(95% CI 0.25–0.65), erlotinib *versus* afatinib 0.41 (95% CI 0.25–0.66); for hypertransaminasemia gefitinib *versus* erlotinib 2.29 (95% CI 1.63–3.23).

Our analysis showed that all treatments had similar efficacy but they differ for toxicities.

Keywords: EGFR-TKI; NSCLC; Review; First line

1. Introduction

Lung cancer is one of the most common and fatal malignancies, accounting for nearly 30% of all cancer-related deaths [1]. Approximately 85% of lung cancers are histologically defined as non-small-cell-lung cancer (NSCLC) and the majority of patients present with advanced disease for which no curative treatment is available [2,3]. The prognosis is poor and the cornerstone still remains a platinum-based-doublet as first-line treatment [4,5].

Activation of the epidermal-growth-factor-pathway may promote tumor growth and progression, stimulating cancer cell proliferation, invasion and metastasis and inhibiting apoptosis, providing a strong rationale for targeting this pathway. In 2004, three groups described activating mutations in advanced NSCLC that make tumors sensitive to EGFR-TKIs [6–8]. The most common activating mutations are in-frame-deletions in exon 19 and the L858R point-mutation in exon 21 [9]. Mutations in exon 18 are rare and mainly activating, while mutations in exon 20 mostly confer resistance to TKIs [10,11]. The discovery that the response to EGFR-TKIs is linked to aberrant EGFR tyrosine-kinase signaling has created a new paradigm for personalizing the treatment of NSCLC. Furthermore, some evidence suggest that mutation in exon 19 is associated to a better outcome when treated with EGFR TKIs when compared to mutation in exon 21 [12,13].

Therefore, several trials addressed the question whether chemotherapy was superior or not to up-front EGFR-TKIs indicating an improvement in PFS and objective response rate (ORR) in patients treated with EGFR-TKIs. No differences in overall survival (OS) were detected, possibly on account of the crossover design. Three EGFR-TKIs have now been developed: gefitinib, erlotinib and afatinib. However, although they all target EGFR, there are differences in terms of toxicity. Therefore, it remains important to identify criteria to help clinicians select the best treatment for EGFR-mutated patients, in terms of efficacy and toxicity in the overall population and according with mutation types.

For this reason, and as there are no direct comparisons of TKIs, we performed a systematic review of the literature and meta-analysis of all phase II/III RCTs in which previously untreated patients with advanced NSCLC were prospectively randomized to receive either EGFR-TKIs as an experimental-arm or chemotherapy as a control-arm.

2. Methods

2.1. Types of study, participant, intervention and outcome

- RCTs in patients of any age and race, with histologically proven NSCLC harboring an activating EGFR-mutation.
- First line EGFR-TKI compared with standard chemotherapy (platinum-based doublet, at any dosage or number of cycles), generally considered of similar clinical efficacy [4].
- PFS as primary outcome; whenever possible only independently reviewed data were extracted.
- Secondary outcomes were PFS in exon 19 deletion, PFS in L858R mutation, OS, ORR (complete and/or partial and/or stable assessed using RECIST criteria) and treatment related toxic events assessed with the NCI CT Criteria.

2.2. Search strategy and selection criteria

PubMed, Cancer-Lit, Embase-databases and Cochrane-Library were searched for RCTs up to June 2014 with no language or publication status restrictions. Search terms were "TKI" [Substance Name] and "Carcinoma, NSCLC" [Substance Name]. The proceedings of the 2008–2014 conferences of the American Society of Clinical Oncology (ASCO), European Society of Medical Oncology (ESMO) and International Association for the Study of Lung Cancer (IASLC), World Conference of Lung Cancer were also searched for relevant abstracts. Any unpublished RCTs were considered for inclusion.

2.3. Data extraction and "risk of bias" assessment

Two review authors (ERH, FA) independently screened the titles and abstracts for inclusion. Full articles or conference proceedings were retrieved for further assessment if the information in the abstract suggested that the study met all the pre-specified criteria. We excluded ongoing studies and studies with not more than ten patients per arm.

Two investigators (ERH, FA) were responsible for data assessment and extraction. We recorded details of study