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Predictors of outcome for patients with lung adenocarcinoma carrying the epidermal growth factor receptor mutation receiving 1st-line tyrosine kinase inhibitors: Sensitivity and meta-regression analysis of randomized trials

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Contents

Abstract

Purpose: We performed a sensitivity and meta-regression analysis, cumulating all randomized trials exploring the benefit of afatinib, erlotinib and gefitinib *versus* chemotherapy in advanced EGFR mutant NSCLC, to investigate the potential role of additional clinico-pathological predictors of TKIs efficacy.

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Results: With regard to progression-free survival (PFS), a significant interaction according to ethnicity (Asian *versus* Caucasian *versus* mixed) and to trial design (retrospective *versus* prospective EGFR analysis), was found; a trend toward significance with regard to type of drug (gefitinib *versus* erlotinib *versus* afatinib) was determined. No statistically significant differences in survival were observed. With regard to response, a significant interaction according to ethnicity, trial design and type of drug, was found.
Conclusion: These data, together with a deeper characterization of the molecular background sustaining the oncogenic process, may contribute to create a clinico-pathologic predictive model, aimed to improve the magnitude of benefit expected from the use of targeted agents.

Keywords: Meta-analysis; Lung cancer; Gefitinib; Afatinib; Erlotinib; Ethnicity; Trial design

1. Introduction

The activating mutations of the epidermal growth factor receptors (EGFR) identify a non-small cell lung cancer (NSCLC) patients' subgroup with a featured prognostic profile [1] and with a peculiar sensitivity to tyrosine kinase inhibitors (TKIs) targeting this pathway [2]. In this context, randomized trials have clearly shown that TKIs may significantly contribute to improve patients' prognosis, disease control, symptoms and quality of life in comparison with standard platinum-based chemotherapy [3–11].

Gefitinib and erlotinib represent nowadays essential therapeutic weapons for the treatment of patients with NSCLC. Their clinical efficacy has been clearly established after the characterization of the appropriate molecular target which allowed to retrospectively distinguish between responding *versus* non-responding patients in the context of the preliminary development conducted in an 'unselected' population [2].

In the absence of a featured molecular predictor, nonsmoking status, female gender, Asian ethnicity and adenocarcinoma histotype have been initially identified as potential prerequisites to achieve response for patients treated with erlotinib and gefitinib [12,13]. Actually, these predictors have been subsequently demonstrated to be just representative of a 'clinically selected' population with a high likelihood of harboring the sensitizing mutation, which represents the key factor for activity and efficacy of TKIs [14]. The type of study design (prospective *versus* retrospective) might represent a predictive factor of drug efficacy because of the relevance of the attrition bias in the context of retrospective trial design [15,16].

It has been widely demonstrated that the majority of the objectives responses to EGFR TKIs are observed in patients harboring somatic mutations of the kinase domain of the EGFR gene, and, in several prospective studies, the presence of these mutations positively correlates with response to EGFR TKIs [2,17]. This benefit in term of response rate have been widely validated by the impressive progression-free survival (PFS) results emerged in EGFR mutant patients, although no advantage in overall survival (OS) has been detected (probably due to the crossover, widely applied in all the trials) [3–11].

In this already 'deeply featured' molecular context, a question arises: is there a rationale justifying a further selection ('super-selection') of EGFR mutant patients on the basis of some demographic or other molecular factors to implement the awaited TKIs benefit? We, therefore, conducted a literature-based meta-regression and sensitivity analyses to investigate the differential effect of TKIs according to potential demographic and molecular factors (which may represent additional predictors of the efficacy of EGFR TKIs in patients with advanced EGFR mutant NSCLC).

2. Materials and methods

The analysis was conducted according to 4 pre-specified steps: (1) definition of the outcomes; (2) definition of the trial selection criteria; (3) definition of the search strategy; and (4) detailed description of the statistical methods used [18,19].

2.1. Outcome definition

Selected outcomes were progression-free survival (PFS), overall survival (OS) and response rate (number of response events in the experimental and control population, ORR). The objective of the current analysis was to perform a:

(1) analysis of heterogeneity among subgroups according to 3 factors: trial design (retrospective *versus* prospective EGFR mutation analysis), predominant ethnicity (Asian *versus* Caucasian *versus* mixed) and drug (gefitinib *versus* erlotinib *versus* afatinib);
(2) meta-regression analysis according to 5 factors, *i.e.* ethnicity (rate of Asian patients), gender (rate of female patients), smoking habit (rate of never smokers), sensitizing mutation type (rate of patients carrying the exon-19 deletion) and rate of patients explicitly receiving second-line TKI.

2.2. Trial identification criteria

All randomized clinical trials (RCT) in which previously untreated patients carrying an activating EGFR mutations (detected either prospectively or retrospectively) with advanced/metastatic NSCLC were assigned to receive Gefitinib (Iressa^{TM}), Erlotinib (Tarceva^{TM}) or Afatinib *versus* chemotherapy, published in peer-reviewed journals or presented at the ASCO, ECCO, ESMO and WLCC meetings until July 1, 2013, were considered.