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Meta-analysis of individual patient data from randomized trials of chemotherapy plus cetuximab as first-line treatment for advanced non-small cell lung cancer

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ABSTRACT

Objectives: Four randomized phase II/III trials investigated the addition of cetuximab to platinum-based, first-line chemotherapy in patients with advanced non-small cell lung cancer (NSCLC). A meta-analysis was performed to examine the benefit/risk ratio for the addition of cetuximab to chemotherapy.
Materials and methods: The meta-analysis included individual patient efficacy data from 2018 patients and individual patient safety data from 1970 patients comprising respectively the combined intention-to-treat and safety populations of the four trials. The effect of adding cetuximab to chemotherapy was measured by hazard ratios (HRs) obtained using a Cox proportional hazards model and odds ratios calculated by logistic regression. Survival rates at 1 year were calculated. All applied models were stratified by trial. Tests on heterogeneity of treatment effects across the trials and sensitivity analyses were performed for all endpoints.
Results: The meta-analysis demonstrated that the addition of cetuximab to chemotherapy significantly improved overall survival (HR 0.88, $p = 0.009$, median 10.3 vs 9.4 months), progression-free survival (HR 0.90, $p = 0.045$, median 4.7 vs 4.5 months) and response (odds ratio 1.46, $p < 0.001$, overall response rate 32.2% vs 24.4%) compared with chemotherapy alone. The safety profile of chemotherapy plus cetuximab in the meta-analysis population was confirmed as manageable. Neither trials nor patient subgroups defined by key baseline characteristics showed significant heterogeneity for any endpoint.
Conclusion: The addition of cetuximab to platinum-based, first-line chemotherapy for advanced NSCLC significantly improved outcome for all efficacy endpoints with an acceptable safety profile, indicating a favorable benefit/risk ratio.

1. Introduction

The treatment of advanced non-small cell lung cancer (NSCLC), which encompasses a number of different histological subtypes [1], remains one of the great challenges of contemporary medical oncology. Approximately 40% of patients with NSCLC present with unresectable metastatic stage IV tumors [2,3]. Systemic chemotherapy (with or without bevacizumab) or tyrosine kinase inhibitor (TKI) therapy (in particular for patients whose tumors have

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activating mutations of the epidermal growth factor receptor gene [*EGFR*]) represent the primary treatment options to extend survival and improve quality of life for this patient group [4–11]. In the majority of patients of good performance status, first-line chemotherapy regimens generally are based on cytotoxic doublets comprising a platinum analog combined with either vinorelbine, gemcitabine, docetaxel, paclitaxel, or pemetrexed (only for patients with non-squamous disease). A series of randomized trials has suggested that the different standard doublets provide similar levels of efficacy in the first-line treatment of NSCLC [12–16].

The addition to first-line doublets of a third, concurrently administered, cytotoxic agent has been shown to increase toxicity without improving overall survival [5,13,17]. However, the phase III First-Line ErbituX in lung cancer (FLEX) trial in patients with EGFR-expressing NSCLC showed that combining the EGFR antibody cetuximab with cisplatin and vinorelbine significantly improved overall survival in this setting (hazard ratio, HR, 0.871, 95% CI 0.762–0.996; $p = 0.044$) [18]. Enrollment of the 1125 patients included in the intention-to-treat (ITT) population of this large multinational trial was independent of NSCLC histology but required some degree of tumor EGFR protein expression. A second phase III trial exploring chemotherapy plus cetuximab in this setting, BMS099, which included an ITT population of 676 patients with advanced NSCLC, reported a survival benefit of similar magnitude for the addition of cetuximab to taxane (paclitaxel or docetaxel) plus carboplatin chemotherapy compared with chemotherapy alone (HR 0.89, 95% CI 0.75–1.05; median 9.7 vs 8.4 months), although in this case, the difference between the treatment arms was not statistically significant ($p = 0.169$) [19]. Tumor EGFR expression was not an eligibility requirement in the BMS099 trial.

We performed a meta-analysis of individual patient data from randomized trials in which chemotherapy plus cetuximab was compared with chemotherapy alone in the first-line treatment of advanced NSCLC. Meta-analyses of individual patient data can offer certain advantages over those based on aggregate or summary data [20]; in particular, the use of individual patient data allows for a more complete analysis, including the study of interaction between the treatment effect and covariates [21]. Our intention was to provide an overall appraisal of the benefit/risk ratio associated with the addition of cetuximab to platinum-based chemotherapy as first-line treatment for advanced NSCLC and to explore treatment outcome in subgroups defined by baseline characteristics of particular interest.

2. Patients and methods

2.1. Selected trials

Four randomized trials which compared platinum-based chemotherapy with or without cetuximab as first-line treatment for patients with advanced NSCLC have been reported [18,19,22,23]. Individual patient efficacy and safety data from these four trials were included in the current meta-analysis. Subsequent electronic searches of publication databases did not identify any relevant additional trials that were eligible for inclusion.

2.2. Individual patient data

Individual patient data were collected for all patients in the ITT and safety populations of the four eligible randomized trials, and included baseline characteristics, best overall response, PFS, overall survival and safety.

2.3. Statistical methods

The primary analysis was the estimation of the overall cetuximab effect based on the four included trials. For the consideration of efficacy endpoints, which were based on the primary definitions in the individual trial protocols, patients were grouped according to randomization, on an ITT basis. The main focus of the efficacy analysis was overall survival, defined as the time between randomization and date of death. A meta-analysis of the incidence of grade 3 or 4 adverse events according to treatment was also carried out and was based on individual patient data from the safety populations of the included trials. The grading of adverse events was performed according to National Cancer Institute – Common Toxicity Criteria (NCI-CTC) v2.0 in the LUCAS and FLEX trials and NCI – Common Terminology Criteria for Adverse Events (CTCAE) v3.0 in the BMS099 and BMS100 trials. Handling rules for NCI-CTC/CTCAE grading were similar across trials, although death related to adverse event was assessed as a grade 5 event in the BMS099 and BMS100 trials. For the purposes of this meta-analysis, in order to allow a comparison between treatment groups of all adverse events that were considered to be severe, including those related to death, grade 5 adverse events in these two trials were summarized together with grade 3 or 4 adverse events. All adverse event evaluations for the meta-analysis were carried out using preferred terms as defined in the Medical Dictionary for Regulatory Activities, v.10.0.

For the overall population and for subgroups defined by baseline factors, HRs for overall survival and PFS were obtained by applying a Cox proportional hazards model stratified by trial and adjusted for selected baseline variables (age, sex, histology, tumor stage (according to TNM Classification of Malignant Tumours, Sixth Edition [24]) and Eastern Cooperative Oncology Group [ECOG] performance status). Unstratified medians and 1-year survival and PFS rates were also calculated. Logistic regression models, stratified by trial and adjusted for the same selected baseline variables, were used to obtain odds ratios for best overall response and the occurrence of grade 3 or 4 adverse events according to preferred terms and composite categories. For response and toxicity, unstratified rates are also given.

In relation to treatment effects, *p*-values were calculated using likelihood-ratio tests for all efficacy endpoints. Interactions between treatment arm and baseline factors with regard to efficacy endpoints were also assessed using likelihood-ratio tests. As all analyses were exploratory, *p*-values were not corrected for the multiplicity of statistical tests. To test for heterogeneity among trials in the adjusted meta-analysis, the adjusted HR of the treatment effect was assessed independently in each trial and the trial HRs were compared using chi-square tests.

Three sensitivity analyses were carried out. These comprised a meta-analysis of individual patient data using a Cox proportional hazards model or logistic regression model stratified only for the factor trial (unadjusted meta-analysis) and a meta-analysis of published estimates of treatment effects across the four trials applying both fixed- and random-effects models. A test of heterogeneity of the treatment effect between trials based on the fixed-effects model was performed, as described [25].

3. Results

3.1. Selected trials and inclusion criteria

Four open-label randomized trials, contributing a total of 2018 ITT patients corresponding to 100% of the randomized patients, were included in the meta-analysis, with 1003 patients randomly