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Docetaxel–carboplatin chemotherapy combined with cetuximab in patients with locally advanced or metastatic non small-cell lung cancer (NSCLC)—Results of the nonrandomised phase II study TaxErb

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ABSTRACT

This open label, single arm phase II study was designed to evaluate the efficacy and safety of the addition of cetuximab to first line chemotherapy with carboplatin and weekly docetaxel in patients with advanced non small-cell lung cancer (NSCLC). From February 2007 to December 2008 74 patients with NSCLC (stage IIIB and IV), ECOG PS ≤2 and no prior systemic chemotherapy were enrolled and treated with carboplatin (area under the curve = 5 on day 1) and docetaxel (35 mg/m^2 on days 1, 8, and 15). Cycles were repeated every 4 weeks for a minimum of 4 and a maximum of 6 cycles. Cetuximab (400 mg/m^2 on day 1 with subsequent doses of 250 mg/m^2 weekly) was administered until progression or intolerable toxicity up to a maximum treatment duration of 12 months. The primary endpoint was the overall response rate (CR + PR) according to RECIST. Secondary endpoints were progression-free survival (PFS), overall survival (OS) and toxicity. Patients received a median of 4 cycles of docetaxel–carboplatin-chemotherapy. The median number of administrations of cetuximab was 14. Sixty-seven patients were evaluable for response. Partial response was seen in 29/67 patients corresponding to an overall response rate (ORR) of 43.3% (95%CI, 28.5–53.7). No patient experienced complete response. The clinical benefit rate (PR + SD) was 79.1%. The 1-year rates for PFS and OS were 11.2% and 64.4%, respectively. Median PFS was 4.8 months (95%CI, 3.70–5.31) and median OS 12.9 months (95%CI 8.26–∞). Adverse events were mainly grades 1–2. Skin toxicity (76% of pts), dyspnea (36.5%) and anemia (31.1%) were most frequent. Results from this phase II study suggest that the addition of cetuximab to first-line doublet carboplatin and weekly docetaxel results in a considerable clinical efficacy with an acceptable toxicity profile for patients with advanced or metastatic NSCLC.

1. Introduction

Lung cancer is the leading cause of cancer death [1]. Despite the huge efforts in optimizing treatment and in particular systemic therapy the overall prognosis remains poor. Chemotherapy with platinum-based doublets is accepted as treatment for patients with advanced and metastatic non small cell lung cancer with good performance status [2]. However, cytotoxic treatment has reached a plateau with PFS in the range of 3.9–6 months and median survival in the range of 1 year [2,3].

One new approach in cancer therapy is individualized treatment to increase efficacy and to reduce side effects. Tumour targets and targeted therapies as well as prognostic and predictive biomarkers are currently being developed.

Epidermal growth factor (EGFR) is overexpressed in 40–89% [4,5] of patients with NSCLC and therefore might be a target for treatment [6–8]. Currently two classes of EGFR-targeting agents are available: the small molecule EGFR tyrosine kinase inhibitors (TKIs) and EGFR-targeted monoclonal antibodies. In NSCLC TKIs are effective as single agents in refractory disease [9,10] but have not shown a benefit when added to first-line platinum combinations in unselected patient populations [11–14]. Gefitinib has demonstrated activity as first-line monotherapy only in specific patient subsets with EGFR mutation [15].

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Cetuximab (Erbitux®) is a monoclonal chimeric IgG1 antibody that blocks EGFR signalling [16]. Furthermore, blocking the receptor leads to internalisation and so reduction of EGFR density on the cell surface. As opposed to the TKI gefitinib sensitivity to cetuximab does not seem to rely on EGFR mutation [17]. Cetuximab may also mediate antitumour immune mechanisms [18,19].

Several phase II trials demonstrated that cetuximab was active in combination with first line platinum chemotherapy in patients with advanced NSCLC [20–25]. Meanwhile two randomized phase III trials have been published. The FLEX trial compared vinorelbine + cisplatin with and without cetuximab [26]. The 1125 patients enrolled had to have immunohistochemical evidence of EGFR expression. Median survival was significantly improved from 10.1 to 11.3 months (HR 0.871, $p = 0.044$) by adding cetuximab and also overall response rates were significantly increased from 29% to 36% ($p = 0.01$). A second trial randomized 676 chemonaive patients with advanced NSCLC to chemotherapy with three-weekly paclitaxel or docetaxel and carboplatin with or without additional cetuximab [27]. Inclusion was not restricted to patients with EGFR-positive tumours. ORR was significantly increased from 17.2% to 25.7% for additional cetuximab while median PFS and OS with 4.4 months and 9.7 months with cetuximab were not as compared to 4.25 and 8.4 months for patients solely treated with chemotherapy.

Weekly docetaxel has been studied extensively as a single agent in second line NSCLC and was shown to have similar efficacy but a significant benefit regarding hematotoxicity as compared to standard docetaxel every 3 weeks [28]. Clinical investigations of platinum and weekly docetaxel in first line therapy of advanced NSCLC have demonstrated good efficacy data combined with a favourable toxicity profile [29–31].

We investigated whether adding the monoclonal anti-EGFR antibody cetuximab to carboplatin and weekly docetaxel may improve the clinical efficacy without increase in toxicity.

2. Patients and methods

This multicentre, single arm, phase II study (EudraCT-Number 2006-004 526 – 90) was conducted at 4 German centres. The study protocol, designed in accordance with the Declaration of Helsinki, was approved by a central ethical review board and the local institutional boards of the participating centres. The study was conducted in compliance with Good Clinical Practice. Patients provided written informed consent before enrolment.

2.1. Patient selection

Patients were eligible if they had histological or cytological evidence of NSCLC stage IIIB or IV, measurable disease according to RECIST [32], a life expectancy of at least 12 weeks, an ECOG performance status of $\leq$2 and adequate hematologic, renal, hepatic and cardiac function. Prior systemic palliative chemotherapy and EGFR-targeted therapy was not allowed, prior neoadjuvant or adjuvant chemotherapy or chemoradiation was allowed if completed $\geq$6 months before enrolment. Patients were not eligible if they had symptomatic brain metastases, prior malignancies other than nonmelanomous skin cancer or curatively treated carcinoma in situ of the cervix, known hypersensitivity to either of the study drugs or were under continuous glucocorticoid medication. Pregnant or lactating women were also excluded.

2.2. Study design

The study was designed as an open label, single arm phase II study. The primary study objective was to evaluate the efficacy of the combination of cetuximab, carboplatin and docetaxel with the primary endpoint defined as the overall response rate (CR + PR) according to RECIST.

Predefined secondary endpoints were the 1-year survival rates, median PFS, median OS and safety.

2.3. Treatment

All patients received carboplatin (AUC5 on day 1, intravenous infusion (IV)) and docetaxel (35 mg/m^2 on days 1, 8, and 15, IV) every 4 weeks until disease progression or intolerable toxicity for a minimum of 4 and a maximum of 6 cycles. Additionally, patients received cetuximab (400 mg/m^2 on day 1 with subsequent doses of 250 mg/m^2 weekly, IV) until progression or intolerable toxicity up to a maximum treatment duration of 12 months.

2.4. Assessments

Efficacy was assessed with chest X-ray, computed tomography or nuclear magnetic resonance tomography and ultrasonography at baseline (within 4 weeks before enrolment) and repeated after cycle 2, 4 and 6, if applicable. After the completion of chemotherapy further assessments were performed according to the local clinical practice of the respective centre and in any case 4 weeks after the last administration of cetuximab. Responses were defined and categorized according to RECIST criteria [32].

Safety assessment including medical history taking, physical examination, and laboratory evaluation was performed using the NCI CTCAE (version 3.0). Prior to treatment study site personnel recorded the occurrence and nature of each patient's pre-existing conditions. During the study, site personnel before each cycle recorded any change in the condition(s) and the occurrence and nature of any adverse events. All adverse events occurring while the patient was receiving study drug were documented in the case report form.

2.5. Statistical methods

The primary efficacy endpoint of this study was ORR according to RECIST criteria. Secondary study endpoints were PFS and OS and assessment of toxicity. Information on progression free and overall survival should comprise 1-year survival rates and median survival. The study was based on Simon's optimized two-stage design [33] using the following 2-step decision strategy.

If in step 1 after 27 patients only 5 patients or less responded, the study would have had to be discontinued. Patient recruitment was to continue if there were more than 5 responders.

If in step 2 after 36 patients only 16 patients or less responded, the treatment regimen would be regarded as ineffective and the study would have had to be discontinued. The trial aim was met successfully whenever 17 or more responders were observed before inclusion of the 63rd patient.

Efficacy analyses were performed in all patients where data on tumour assessments were available and evaluation of response as per RECIST criteria feasible. Median PFS and OS were calculated using Kaplan–Meier estimates. Analyses of safety and dosing included all patients receiving at least one cycle of study drug treatment.

3. Results

3.1. Patients

From February 2007 to December 2008 75 patients with advanced or metastatic NSCLC were recruited.

In September 2008 the interim analysis requested for step one of the Simon stage 2 design exhibited 11 responders in the first