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Efficacy and safety of rechallenge treatment with gefitinib in patients with advanced non-small cell lung cancer

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ABSTRACT

Objectives: Although patients with advanced non-small cell lung cancer (NSCLC) and an activating epidermal growth factor receptor (EGFR) mutation benefit from the use of EGFR-tyrosine kinase inhibitors (TKI), most of them progress within 12 months from treatment start due to acquired resistance. In clinical practice, many physicians frequently offer these patients retreatment with EGFR-TKIs after a chemotherapy break, based on small or retrospective studies.

Materials and methods: A phase II trial was conducted in patients with stage III/IV NSCLC, to assess the efficacy, safety and impact on quality of life (QoL) and disease-related symptoms of gefitinib rechallenge. Eligible patients had initially responded to first-line gefitinib and progressed after second-line chemotherapy.

Results: Of 61 enrolled patients, 73.8% were female, 100% had EGFR-mutated adenocarcinoma and 67.2% were never-smokers. Thirty-two (52.5%) patients obtained a clinical benefit, with 3 (4.9%) achieving a partial response and 29 (47.5%) having stable disease. Median progression-free survival was 2.8 months, overall survival 10.2 months and duration of gefitinib treatment 3.6 months. The most common all grade-adverse events were diarrhea (27.6%), nausea and/or vomiting (20.3%), rash (14.7%) and dyspnea (10.3%); no new toxicities were apparent.

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Conclusion: Findings from this study indicate that gefitinib rechallenge offers modest benefit and may be taken into consideration only for patients for whom no other treatment option exists.

1. Introduction

To date, lung cancer remains the most frequently diagnosed malignancy and the leading cause of cancer death worldwide [1]. Approximately 80% of patients are diagnosed with non-small cell lung cancer (NSCLC) and about 55% of these present with locally advanced or metastatic disease, the 5-year survival rate being <5% [2]. Indeed, in these patients, therapy aims to prolong survival while improving health-related quality of life (QoL) and cancer-related symptoms [3]. The choice of optimal therapy takes into account different factors, such as tumour histology [4,5] and the presence of mutations [6]. In particular, the frequent deregulation of epidermal growth factor receptor (EGFR) [7,8] has prompted the development of EGFR-targeted therapies, that have indeed improved the management of certain patient subsets.

Gefitinib, a potent and selective first-generation EGFR-tyrosine kinase inhibitor (TKI) has shown superiority for progression-free survival (PFS) in first-line phase III trials in patients with EGFR mutations (EGFR-M+), compared to platinum-based doublet chemotherapy (CT). Indeed, the IPASS study reported a median PFS of 9.5 months following treatment with gefitinib vs 6.3 months with CT ($p < 0.0001$) [9], the NEJ002 study 10.8 vs 5.4 months, respectively ($P < 0.001$) [10] and the WJTOG3405 study 9.2 vs 6.3 months ($P < 0.0001$) [11]. Regarding overall survival (OS), no significant difference was reported following gefitinib and CT [9–11] or placebo [12] but, compared to the latter, gefitinib provided a benefit in never-smokers (OS: 8.9 vs 6.1 months, respectively, $P = 0.012$) and in patients of Asian origin (OS: 9.5 vs 5.5 months, $P = 0.01$) [12].

A major concern remains acquired resistance to TKIs, as it leads to disease progression within one year from the start of treatment in the vast majority of initial responders [13]: in this scenario, in which no standard of care exists for patients who have already received an EGFR-TKI, establishment of salvage treatment is an urgent issue. The mechanisms responsible for resistance are complex and heterogeneous (e.g. SCLC transformation, epidermal to mesenchimal transition, HER2 amplification/mutation and cMET amplification [14–20]), but in approximately 50% of cases it relies on the T790M mutation, which in some patients is already present at low levels before TKI treatment [21]. Actually, new agents such as osimertinib (AZD9291), rociletinib and HM61713 have shown activity in NSCLC patients with the EGFR T790M mutation who failed prior EGFR-TKI [22–24], but, except for osimertinib that has recently received approval in the US and in Europe, these drugs have not been approved yet. Indeed, compelling evidence has pointed towards the coexistence of sensitive and resistant clones in NSCLC: upon TKI administration, a fraction of sensitive cells is eradicated, whereas resistant clones proliferate, leading to clinical resistance. Second-line cytotoxic CT acts on these cells while sparing TKI-sensitive clones, whose re-growth leads to progressive disease. However, as they retain sensitivity to TKI, subsequent rechallenge with the inhibitor should provide clinical benefit [17,25–30]. Few studies have assessed the efficacy and safety of second-line cytotoxic therapy after development of TKI resistance, and contrasting data have been published on the influence of a prior treatment with TKI on subsequent CT [31,32]. Notably, a recent multicenter, retrospective study has shown significantly prolonged PFS in EGFR-M+ NSCLC patients who failed first-line TKI and underwent second-line pemetrexed monotherapy ($n = 37$), compared to platinum-based doublet CT ($n = 46$; 4.2 vs 2.7 months, respectively, $P = 0.008$) [33].

Encouraging results have been obtained by re-administering gefitinib to NSCLC patients who have progressed following second-line CT after failure of initial TKI treatment [34–38], but a prospective study testing this strategy in a sufficient number of patients is still lacking. The ICARUS (Iressa re-Challenge in Advanced NSCLC EGFR-M+ patients who Responded to gefitinib USed as first-line or previous treatment) study assessed the efficacy and safety of gefitinib rechallenge in 61 selected patients with advanced stage EGFR-M+ NSCLC, who achieved objective response upon first-line gefitinib and subsequently progressed following CT.

2. Methods

2.1. Study design

ICARUS trial (NCT01530334) is a phase II, open label, multicentre, single arm study conducted to investigate the efficacy, safety and tolerability of oral gefitinib 250 mg/day as treatment rechallenge in patients with EGFR-M+ locally advanced or metastatic NSCLC, who responded to first-line gefitinib and progressed after second-line CT.

Primary end-points were objective response rate (ORR) and clinical benefit rate (CBR). Secondary end-points included PFS, duration of therapy and overall survival (OS). Pre-planned exploratory objectives comprised assessment of QoL and symptom improvement during gefitinib treatment and 4 weeks post-progression.

2.2. Patient population

Inclusion criteria were: age ≥18 years; life expectancy ≥12 weeks; histologically or cytologically confirmed EGFR-M+ locally advanced or metastatic stage IIIB/IV NSCLC unsuitable for therapy of curative intent; a previous first-line treatment with gefitinib with a documented complete response (CR) or partial response (PR) or stable disease (SD) >12 weeks as the best response; progression during or after a subsequent CT; World Health Organization (WHO) performance status (PS) of 0–2 [39]; measurable disease defined according to Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1 [40].

Exclusion criteria included any history of interstitial lung disease, inadequate organ function, symptomatic brain metastases, any unresolved chronic toxicity greater than Common Toxicity Criteria (CTC) grade 2 from previous anti-cancer therapy, and any evidence of severe or uncontrolled systemic disease.

All patients provided informed consent prior to any study specific procedures. Study approval was obtained by independent ethics committees at each institution. The study was conducted in accordance with the Declaration of Helsinki.

2.3. Treatment

Patients received gefitinib (250 mg/day orally) until objective progression of disease (PD), discontinuation for toxicity or consent withdrawal. After progression, patients could receive gefitinib for as long as they were deriving clinical benefit (CB) as judged by the investigator. After discontinuation, further treatments were