Targ Oncol
DOI 10.1007/s11523-010-0163-4

ORIGINAL RESEARCH

Activity and safety of erlotinib as second- and third-line treatment in elderly patients with advanced non-small cell lung cancer: a phase II trial

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Received: 29 January 2010 / Accepted: 2 July 2010

Abstract Erlotinib is an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor. Efficacy of this drug was documented in the BR.21 trial showing that adenocarcinoma, female gender, Asian ethnicity and never-smoker status are predictive of clinical response to erlotinib. Retrospective studies documented the same benefits for elderly patients as young patients in terms of response, progression-free survival, and overall survival. The primary aim of our trial was to confirm these findings in a prospective way; the secondary aim was to identify if the aforementioned clinical characteristics may be predictive of response even in elderly patients. The trial included 31 patients with pretreated stage IIIB (2) and IV (29) non-small cell lung cancer (NSCLC). Median age was 75 years (range: 65–85). Twenty-seven patients were current/former-smokers and four never-smokers. Twenty-three patients are evaluable for response. Objective response rates were reported in five patients (16%). Five patients had stable disease (16%) and 13 progressive disease (43%). Seven patients had a "clinical benefit" from erlotinib (22.5%; 95% C.I.: 7.9–37.2%). Grade 3 skin rash was recorded in three patients (10%). Median survival was 9 months (range 1–30). Median time to progression was 3 months (range: 1–24 months). Our study confirmed erlotinib activity and safety as second- and third-line treatment in elderly patients with advanced NSCLC, especially in terms of median survival. Even though this trial does not allow us to draw a definitive conclusion about the role of a particular clinical characteristic predictive of response, the "clinical benefit" was documented especially in females, in patients with adenocarcinoma histology and skin rash, confirming previous retrospective data.

Keywords Erlotinib · NSCLC · Elderly

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Introduction

Lung cancer is the most common cause of cancer death worldwide. In the United States, there were estimated to be over 200,000 new cases and 160,000 deaths in 2007 [1]. The median age at diagnosis is now 70 years, unlike in the 1970s when it was 64 years; moreover, about 75% of these patients have advanced disease. Therefore, in recent years the treatment of elderly patients with non-small cell lung cancer (NSCLC) has become a real challenge for the oncologists. Unfortunately, active treatments for older patients have been simply extrapolated from phase II and III studies, based on the consideration that elderly patients are under-represented in clinical trials, where only 25% to 32% of participants are over 65 years compared with 61% to 63% of all patients with cancer [2, 3]. Prospective data in the elderly population derived especially from two Italian phase III trials: in the ELVIS study [4], a monotherapy with vinorelbine demonstrated a significant survival benefit over best supportive care in patients ≥70 years; in the MILES study, Gridelli C et al. [5] documented that gemcitabine monotherapy had similar efficacy as vinorelbine without incremental benefit using the drugs in combination.

Published online: 02 October 2010

The difficulty in treating elderly patients with NSCLC rises when one looks to choose a second-line treatment after progression following a first chemotherapy regimen. Docetexel for squamous [6, 7] and pemetrexed for non-squamous histology [8] are the second-line chemotherapy options; the biological agents approved in United States and Europe for the treatment of recurrent NSCLC are erlotinib [9] and, recently, gefitinib (only in patients with epidermal growth factor receptor [EGFR] mutations) [10]. In the BR.21 trial, erlotinib was compared with placebo as second- and third-line therapy, with a significant benefit in overall survival (6.7 versus 4.7 months) and quality of life [9]. Recent subgroup analysis of BR.21 [11] documented that there was no significant difference between age groups randomly assigned to erlotinib or placebo in response, progression-free survival, or overall survival. However elderly patients, compared with young patients, had significantly more overall and severe (grade 3 and 4) toxicity (35% versus 18%), were more likely to discontinue treatment as a result of treatment-related toxicity (12% versus 3%), and had lower relative dose-intensity.

Another retrospective analysis of chemotherapy-treated NSCLC patients in the Taiwan Erlotinib Access Program [12] demonstrated that age ≥65 years was a predictor of low response rate in multivariate analysis (response rate 20.4% in patients age ≥65 years versus 34.4% in patients age <65); however, the disease-control rates of the two groups were similar (72.6% in patients ≥65 years versus 73.1% in patients age <65). The lack of prospective data in elderly patients with recurrent NSCLC treated with erlotinib induced us to start a phase II study with the primary aim to explore the "clinical benefit" of this drug, confirming results of retrospective trials. The secondary aim was to analyze clinical characteristics of patients in order to identify if female gender, adenocarcinoma histology, and smoking habit might be predictive of response to erlotinib in this population.

Patients and methods

Eligibility criteria

Consecutive patients with cytologically and histologically measurable stage IIIB to IV NSCLC entered the study. All patients had to be ≥65 years and pretreated at least with one line of chemotherapy. Other selection criteria included [a] Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) 0–3, [b] adequate liver, renal, and bone marrow function, and [c] life expectancy of at least 2 months. Patients with symptomatic brain metastases were included in the study. Staging procedures included physical examination, complete blood cell count and chemistry, chest and upper abdomen computed tomography (CT) scan and bone scan; brain CT scan was performed if clinically indicated. Written informed consent was obtained from all patients.

Study design and statistical methods

Erlotinib (Tarceva®, Roche) was administered at the dose of 150 mg once a day until progression or unacceptable toxicity. The aims of the study were activity and toxicity of erlotinib in locally advanced (IIIB) and metastatic (IV) NSCLC. Activity was considered be of "clinical benefit" when there was objective response plus stable disease ≥6 months. Response to therapy was assessed according to World Health Organization (WHO) standard criteria [13] after the first 2 months of erlotinib administration and then every 2 months; only patients with stable disease or objective response carried on treatment. Toxicity was evaluated every month according to version 3.0 National Cancer Institute (NCI) Common Toxicity Criteria (CTC). Time to progression was calculated from day 1 of erlotinib administration to the first documentation of progression; overall survival was calculated from day 1 of erlotinib administration to the date of death or, in absence of its assessment, last follow-up. Median time to progression and median survival were calculated according to the Kaplan-Meyer method. According to Simons' optimal two-stage design, for a target activity level of at least 20% in terms of "clinical benefit", if no objective response was documented after the first 12 evaluable patients the drug was considered inactive (alfa and beta error probabilities 0.10 and 0.10, respectively).

Results

Thirty-one patients (pts) with pretreated stage IIIB (2 pts) and IV (29 pts) NSCLC entered the study. There were 28 males and 3 females. PS was as follows: 0 in 4 patients, 1 in 15 patients, 2 in 10 patients, and 3 in 2 patients. Histological types were: 13 adenocarcinoma, 10 squamous, 2 adenosquamous, 2 anaplastic, 2 bronchiolo-alveolar, and 2 unspecified non-small cell. Median age was 75 years (range: 65–85). Fifteen patients were pre-treated with 1 line, 15 patients with 2 lines and 1 patient with three lines of treatment; 24 patients (77%) received platinum-based chemotherapy. Twenty-seven were current or former-smokers and four never-smokers. Patient characteristics are summarized in Table 1.

Twenty-three patients were evaluable for response and all for toxicity (Table 2). Objective response rate was documented in five patients (16%), according intention-to-treat analysis; 5 had stable disease (16%) and 13 progressive disease (43%). Seven patients had a "clinical benefit" (complete/partial response + stable disease ≥6 months)

Table 1 Patient characteristics

Characteristics	Number of patients
Patients enrolled	31
Median Age, years (range)	75 (65–85)
Disease stage	
IIIB	2
IV	29
Performance status	
0	4
1	15
2	10
3	2
Current/former smokers	27
Never smokers	4
Previous chemotherapy	
1 line	15
2 lines	15
3 lines	1
Histological types	
Adenocarcinoma	13
Squamous	10
Anaplastic	2
Mixed (adeno-squamous)	2
Bronchiolo-alveolar	2
Unspecified non-small-cell	2
Metastatic sites	
Lung	13
Bone	12
Pleural effusion	7
Lymph nodes	5
Liver	3
Adrenal gland	2

Table 2 Results and toxicity

Results	Number of patients (%)
Evaluable for response	23
Evaluable for toxicity	30
Objective response	
Partial Response	5 (16%)
Stable disease	5 (16%)
Progressive disease	13 (43%)
"Clinical benefit" (partial response + stable disease ≥6 months)	7 (22.5%)
Toxicity	
Grade 2 ocular toxicity	3 (10%)
Grade 2–3 skin rash	9 (29%)
Grade 3 liver toxicity	1
Dose reduction	6 (19%)

from erlotinib (22.5%). Grade 3 skin rash was recorded in 3 patients (10%) and grade 2 in 6 patients (19%), 1 patient experienced grade 3 liver toxicity and 3 patients had grade 2 ocular toxicity; no episodes of grade 2–3 diarrhea were reported. Six patients (19%) needed a dose reduction to 100 mg daily: 4 patients for skin rash, 1 for grade 3 liver toxicity, and 1 for ocular toxicity. Median time to progression was 3 months (range 1–24) (Fig. 1). Median survival was 9 months (range 1–30) (Fig. 2). Clinical benefit was documented especially in females (all three women responded), in patients with adenocarcinoma (6 out of 7 patients), and in patients with skin rash (6 out 7). No difference was recorded between smokers (4 responses) and never-smokers (3 responses) (see Table 3). Two patients did not perform the first instrumental evaluation (6%) at the time of data analysis. Six patients were not evaluable for response (16%) for other reasons: two patients took only a few erlotinib tablets; in two patients a comparison with the previous CT-Scan was not performed; another two patients did not come back to our institution after the first erlotinib administrations.

Discussion

Monotherapy with vinorelbine or gemcitabine is the best choice for the first-line treatment of the elderly [4, 5], even though a schedule with a platinum-derivate combination can be offered to "fit" patients [14]. Moreover, a Cancer and Leukemia Group B trial comparing paclitaxel with paclitaxel and carboplatin showed an improved response rate and failure-free survival in the combination arm but no overall survival benefit. Stratification by age (<70 and >70) was performed in the elderly group: the results were similar regardless of age group [15].

The decision about a second or third line of treatment is harder considering that many of these patients have poor

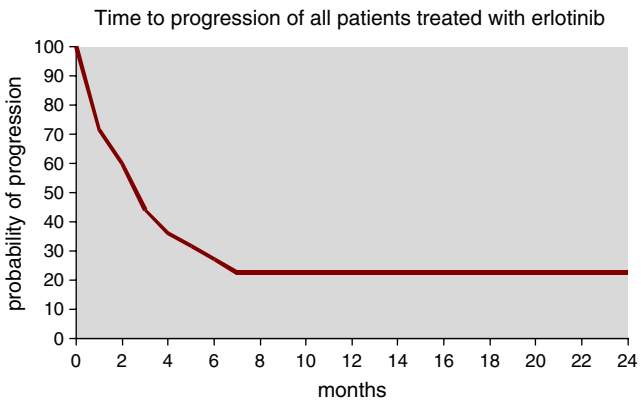

Fig. 1 Time to progression of all patients treated with erlotinib

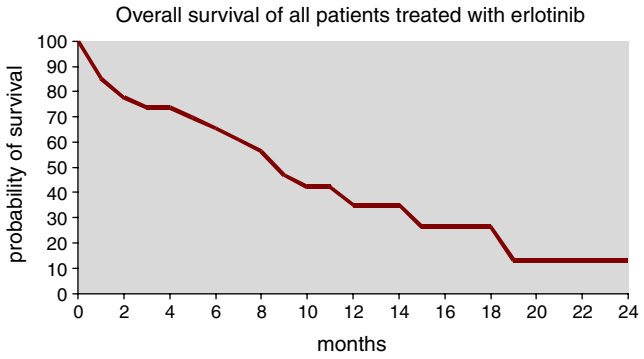

Fig. 2 Overall survival of all patients treated with erlotinib

performance status and co-morbidities that may preclude the use of a number of drugs. In fact, some authors postulated that performance and co-morbidity index are more important prognostic markers than age alone, suggesting that chronologic age may be more predictive of outcome and tolerance to treatment [16, 17]. Docetaxel [6, 7] and pemetrexed [8] have been approved for second-line treatment with a better safety profile for pemetrexed; moreover, a retrospective analysis did not find any difference in efficacy and toxicity between the two age groups (<70 and >70) [18]. Recently, this drug demonstrated better activity on NSCLC with non-squamous histology and its administration has been permitted only in these tumors [19].

In 2005, the BR.21 trial [9] documented activity of a new biological agent, erlotinib, which interferes with epidermal growth factor receptor (EGFR) activity. EGFR is a member of the ErbB-family of cell membrane receptors that are important mediators of cell growth, differentiation, and survival [20]. This receptor is a transmembrane glycoprotein, which consists of an extracellular domain that recognizes and binds specific ligands, and an intracellular domain that contains the tyrosine kinase activity—erlotinib works through the inhibition of this domain. A retrospective analysis of the BR.21 trial in the elderly [11] demonstrated no significant difference between age groups in terms of response, progression-free survival, or overall survival even though more side effects were reported in this subgroup of patients.

Another retrospective analysis of chemotherapy-treated NSCLC patients in the Taiwan Erlotinib Access Program [12] demonstrated that age ≥65 years was a predictor of low response rate in multivariate analysis; however, the disease-control rates of two groups were similar. These two retrospective studies published in 2008 documented that erlotinib can be a good option in elderly patients who progressed to a first-line treatment but, meanwhile, no prospective data has been published in recent years to confirm these results.

In January 2007, we decided to start a phase II study with the aim to explore, in a prospective fashion, activity and safety of erlotinib on elderly patients with advanced NSCLC progressed after one or more chemotherapy lines. Our study confirmed activity of the drug in terms of "clinical benefit" (objective response and stable disease ≥6 months), which we consider a better evaluation as compared with the only response rate. It is well known that biological agents, due to their particular mechanism of action, often obtain longer disease stabilization, which is more important than a simple objective response. Clinical benefit was documented in seven patients (22.5%) and objective response in five patients (16%), according intention-to-treat analysis. These results are encouraging and are consistent with the BR.21 trial, considering that in phase III trials the response rates are always lower than in phase II studies. Median survival was 9 months, higher than reported in the phase III studies with docetaxel (7.5 and 5.7 months in TAX 317 and TAX 320, respectively), pemetrexed (8.3 months) or erlotinib (6.7 months); obviously, this data should be considered with caution since survival cannot be the aim of a phase II non-randomized study. Concerning toxicity, no grade 2–3 diarrhea was recorded; skin rash was the main side effect in 48.3% of patients (grade 3 in 10% of patients). Only six patients (19%) needed a dose reduction, mainly due to skin rash (4 out of 6). These toxicities do not differ from other studies [9, 10]. In BR.21 trial [9], grade 3–4 skin rash and diarrhea were reported in 9% and 7% of patients, respectively; in retrospective analysis of the same study on elderly patients [10], the percentage were 16% and 7%. Therefore, these data confirm the safe toxicity profile of erlotinib that make this drug a good option for the treatment of elderly patients after the first line.

Exploring the relationship between response and clinical characteristics, we think that no patients should be excluded from erlotinib administration even though being female,

Table 3 Characteristics of seven patients with "clinical benefit" to erlotinib (partial response + stable disease ≥6 months)

Gender		Smoking		Histology		Skin rash	
Male	Female	Current/former smokers	Never smokers	Adenoca./Adenosquamous	Squamous	Yes	No
4	3	4	3	6	1	6	1

having adenocarcinoma and skin rash were good predictors of response in our trial, confirming previous data. In our study the patient who survived the longest (30 months) was a man, smoker, with squamous cell carcinoma; in fact, if this type of patient is not considered an ideal candidate for erlotinib, the BR.21 trial demonstrated that in this group, the median survival time was significantly longer in patients receiving erlotinib than in patients with similar characteristics in the placebo arm. Therefore, we may conclude that our study just confirms activity of erlotinib in elderly patients and the importance of some clinical characteristics to predict response.

Conflict of interest statement No funds were received in support of this study and no benefits in any form have been or will be received from a commercial party related to the subject of this paper.

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