J BUON 2013; 18(1): 188-194
ISSN: 1107-0625 www.bu-on.org/jbuon
E-mail: jbuon@ath.forthnet.gr

ORIGINAL ARTICLE

Phase II study of erlotinib plus gemcitabine in first-line treatment of poor prognosis, advanced non-small cell lung cancer patients

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Summary

Purpose: The purpose of the present trial was to investigate whether clinical benefit can be obtained by concurrent administration of erlotinib with gemcitabine as first-line treatment in patients with advanced non-small cell lung cancer (NSCLC) and ECOG performance status (PS) 2.

Methods: Included were chemotherapy-naive patients with histologically/cytologically documented unresectable advanced and/or metastatic (stage IIIB/IV) NSCLC and ECOG PS 2. In this phase II, single-arm study, all patients received first-line gemcitabine plus erlotinib for 6 cycles or until disease progression, unacceptable toxicity or patient withdrawal due to any reason. The primary study objectives were the evaluation of disease response and the time to progression. Secondary objectives included evaluation of overall survival and the safety profile of gemcitabine plus erlotinib.

Results: Nineteen eligible patients were studied. The overall response rate (complete response/CR and partial response/PR) was 15.8% and the clinical benefit rate (CR+PR+stable disease/SD) 36.84%.The median overall survival for the whole study group was 39 weeks (95% CI 27-51) and the median time to disease progression for 19 evaluable patients was 15 weeks (95% CI 7-36). The safety profile of the combination was acceptable with only 2 serious adverse events.

Conclusion: Taking into account similar published clinical studies we conclude that gemcitabine plus erlotinib achieve superior response rate and comparable overall survival with acceptable toxicity compared to monochemotherapy with gemcitabine. This combination represents a treatment option for patients with advanced NSCLC and ECOG PS 2.

Key words: erlotinib, gemcitabine, non small cell lung cancer, poor performance status

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Received: 13/01/2012; Accepted: 22/02/2012

Introduction

Lung cancer is the major cause of cancer-related deaths in North America and Europe [1]. Most patients die as a consequence of their disease within 2 years of diagnosis. NSCLC patients is the most common type of lung cancer, accounting for approximately 80% of the cases. For many NSCLC patients, successful treatment remains elusive. About 70% of all NSCLC patients have advanced-stage disease at diagnosis. Advanced tumors often are not amenable to surgery and may also be resistant to radiotherapy and chemotherapy. Systemic chemotherapy is the standard treatment for this group of patients. The aims of therapy for advanced-stage disease include survival prolongation, symptom relief and improvement of quality of life. The therapeutic benefits of therapy must be balanced against by the potential treatment-related toxicity.

The average age of patients diagnosed with lung cancer is 70 years [2]. Age alone is not a predictor of response or survival in advanced NSCLC; however, poor ECOG PS score of 2 or more, is a prognostic factor for survival and tolerability of chemotherapy [3,4]. Patients with PS 2 score have some restrictions in their physical activity, are unable to work, and spend up to half their waking hours resting or in bed [4]. As many as 40% of patients with advanced NSCLC have poor PS, and these patients are often excluded from clinical trials [4]. They tend to have poorer responses to treatment and shorter survival than their counterparts with PS score of 0–1. It is also generally believed that they are at greater risk for toxicity [4].The treatment of patients with ECOG PS 2 is poorly defined. However, such patients represent a large cohort of the overall lung cancer population.

Our aim was to investigate if clinical benefit can be obtained by concurrent administration of erlotinib in combination with gemcitabine as first-line treatment in advanced, unresecable NSCLC patients with ECOG PS 2.

Methods

Study objectives

The primary objectives of the study were to evaluate the time to disease progression and the response rate (CR,PR), assessed according to RECIST criteria. The secondary objectives were to evaluate the overall survival and the safety profile of erlotinib plus gemcitabine.

Inclusion criteria

Eligibility was restricted to adults patients with histologically/cytologically documented advanced and/or metastatic (stage IIIB/IV), chemotherapy-naive, unresectable NSCLC. Other inclusion criteria were evidence of disease with at least one measurable lesion evaluated on RECIST criteria, age 18 years or older, ECOG PS 2, life expectancy of at least 12 weeks, patients without previous systemic chemotherapy or radiation therapy or immunotherapy and who, in the opinion of the investigators, were not suitable for surgery. Patients should have granulocyte count > 1.5 x 10^9/L and platelet count > 100 x 10^9/L, serum bilirubin < 1.5 the upper limit of normal (ULN),AST and/or ALT < 2 x ULN (or < 5 x ULN if clearly attributable to liver metastasis), serum creatinine < 1.5 ULN or creatinine clearance > 60 ml/min.

Exclusion criteria

Exclusion criteria included any active, non-controlled systemic disease, prior therapy with HER1/EGFR inhibitors, any other malignancies within the previous 5 years (except adequately treated carcinoma *in situ* of the cervix or basal or squamous cell skin cancer), brain metastasis or spinal cord compression, any significant ophthalmologic abnormality, patients who could not take oral medication, and nursing mothers.

The study was approved by the National Ethics Committee and by the Regulatory Authority from Romania and all patients gave written informed consent to participate in the study.

Study design

The study had a treatment phase and a survival follow-up phase. In the treatment phase, all patients received gemcitabine 1000 mg/m^2 in 250 ml N/S over 30 min on days 1, 8 and 15 (q28 days) plus erlotinib 150 mg/day p.o. as first-line treatment of NSCLC. The treatment was administered for 6 cycles or until disease progression, unacceptable toxicity or patient withdrawal due to any reason. Subjects who experi-

enced progressive disease entered the survival follow-up phase for survival estimation and additional NSCLC treatment unless they withdrew their consent to continue in the study or were lost to follow-up.

Data collection

Baseline staging consisted of full medical history, clinical examination, ECOG PS, chest and abdominal CT scan, electrocardiogram, blood counts and serum biochemistry. During the study, before each chemotherapy cycle an evaluation was performed including physical examination, routine hematological and biochemical parameters, change in smoking status and determination of changes in PS; disease assessment was done according to RECIST criteria using CT scan of the thorax and upper abdomen every 8 weeks during treatment and after treatment completion.

All adverse events encountered during the treatment period were recorded. Their intensity, duration, their relationship with the study medications, any treatment given for an adverse event, as well as the outcome of the adverse event were recorded. Grading of all adverse events was done according to the NCI Common Toxicity Criteria for Adverse events, version 3.0, on a 5-point scale (grade 1 to 5).

Statistics

The primary efficacy variable was time to disease progression, which was defined as the interval between the date of response to treatment to the date of the first documentation of disease progression. Objective response rate (CR+PR) were assessed by the RECIST criteria. Overall survival was defined as the interval between the date of the patients' entry into the study and the date of death from any cause. Patients who were alive at the time of analysis were censored at the date of the last follow up assessment. Patients without follow up assessment were censored at the day of last dose of treatment and patients with no post baseline information were censored at the time of study entry.

Categorical data were presented as absolute numbers and as percents, while quantitative data as median with 95% confidence intervals (95% CI) and the corresponding survival range. Survival analysis was performed using the Kaplan-Meier method and curves were compared by two-sided log-rank test. Comparison was performed only for the survival in relation to histological type (squamous cell vs non-squamous cell carcinomas). A p value of ≤0.05 was used to indicate statistical significance. All statistical analyses were carried out using STATA/SE 11 software (Statacorp, College Station, TX, USA).

Table 1. Patient characteristics

Characteristics	*N (%)*
Median age, years (range)	64 (47-75)
Gender	
Male	16 (84.21)
Female	3 (15.79)
Pathological subtype	
Squamous cell carcinoma	7 (36.84)
Adenocarcinoma	9 (47.37)
Bronchoalveolar carcinoma	1 (5.26)
Large cell carcinoma	2 (10.53)
TNM stage	
IIIB	7 (36.84)
IV	12 (63.16)
Number of metastatic sites	
2	11 (57.89)
3	6 (31.58)
4	1 (5.26)
5	1 (5.26)
Metastatic sites localization	
Lung*	19 (100)
Skin	1 (5.26)
Bone	3 (15.79)
Brain	0 (0.00)
Abdomen	5 (26.32)
Pelvis	2 (10.53)
Smoking status	
Ex-smokers	6 (31.58)
Current smokers	7 (36.84)
Never smokers	3 (15.79)
Not known	3 (15.79)

*homolateral or contralateral intrapulmonary metastases

Results

Between August 2008 and April 2010, 20 Caucasian patients meeting the inclusion criteria were studied. One patient wasn't included in the final analysis. Median age was 64 years (range 47-75), and males prevailed (84.21%). Of the patients 68.42% were ex

Table 2. Concomitant diseases

Concomitant diseases	*N (%)*
Arterial hypertension	8 (42.11)
Ischemic cardiac disease	4 (21.06)
Chronic heart failure	3 (15.79)
Obliterated arteriopathy	2 (10.53)
Atrial fibrillation	1 (5.27)
Mitral insufficiency	1 (5.27)
Chronic obstructive pulmonary disease	3 (15.79)
Asthma	1 (5.27)
Pulmonary tuberculosis	1 (5.27)
Liver cirrhosis	2 (10.53)
Chronic renal failure	1 (5.27)
Diabetes mellitus type 2	2 (10.53)
Dyslipidemia	2 (10.53)
Obesity	1 (5.27)
Hyperthyroidism	1 (5.27)
Irritable bowel disease	1 (5.27)
Lumbar spondylitis	1 (5.27)
Prostatic neoplasm	1 (5.27)
Sarcoidosis	1 (5.27)
Allergic dermatitis	1 (5.27)

Table 3. Follow-up duration (weeks) after the end of treatment for 13 patients

Median	*Minimum*	*Maximum*
13	4	36

smokers and current smokers.The most frequent localizations of metastases were in the lung. Most patients had multiple metastatic sites. The main patient characteristics are listed in Table 1.

Concomitant diseases were recorded for every patient. Cardiovascular abnormalities, especially high blood pressure and ischemic cardiac disease prevailed (Table 2) and follow-up information is displayed in Table 3.

Treatment duration

The treatment duration was calculated from the day 1 of the first cycle until the end of treatment or the data mentioned in survival visit for the 2 lost patients. The median duration of treatment was 10 weeks (range 2-26); the median duration of investigation (treatment + follow-up) for 19 patients was 24 weeks (range 2-50). The median duration of erlotinib administration was 9 weeks (range 1-22) and the median number of gemcitabine cycles received was 7.5 (range 1-22). Four out of 19 patients (21.05%) completed the 6 study treatment cycles.

Table 4. Response to therapy according to RECIST criteria

Response	*N*	*%*
Partial response	3	15.79
Stable disease	4	21.05
Progressive disease	8	42.11
Not evaluated	4	21.05

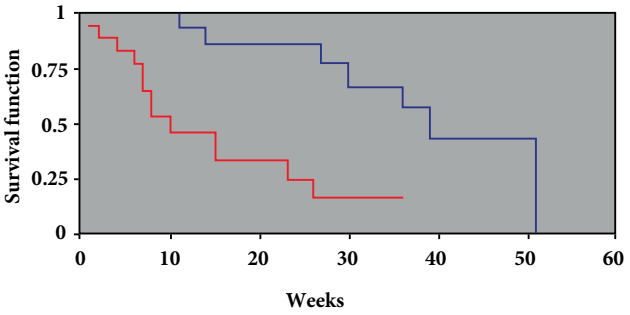

Figure 1. Overall survival and time to disease progression.

— Overall survival for all patients (N=19)
— Time to progression (N=18)

Overall survival, median/weeks (95% CI): 39 (27-51).
Time to progression, median/weeks (95% CI): 15 (7-36).

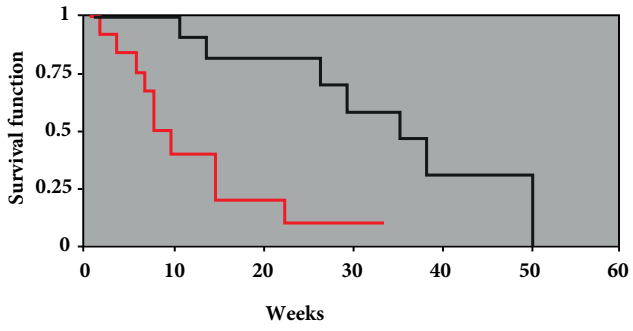

Figure 2. Overall survival and time to disease progression for smokers.

— Overall survival for smokers (N=13)
— Time to progression for smokers (N=13)

Overall survival, median/weeks (95% CI): 36 (14-40).
Time to progression, median/weeks (95% CI): 13 (4-15).
Overall survival and time to progression between smokers (Figure 2) vs the whole study group (Figure 1) did not differ significantly (log-rank p=0.8201 and p=0.6619, respectively).

Response to treatment

The overall response rate was 15.8 % and the clinical benefit rate 36.84% . Four patients were not assessed: 3 patients were lost during the first cycle and one patient was lost at the beginning of the second cycle of treatment (Table 4).

The median overall survival for the complete study population (N=19) was 39 weeks (95% CI: 27-51) and the median time to disease progression for 18 evaluable patients was 15 weeks (95% CI:7-36) (Figure 1).

For smokers (13 patients former or current smokers), the median overall survival was 36 weeks (95% CI: 14-40) and the median time to disease progression 13 weeks (95% CI:4-15), both lower than the median overall survival (p=0.8201) and median time to disease progression (p=0.6619) for the entire group (Figure 2). For non smokers no analysis was done because there were only 3 non smokers and 3 patients who did not declare their smoking habits.

Kaplan-Meier overall survival between patients with squamous cell vs non squamous cell carcinoma did not differ significantly (p=0.9361; Figure 3).

Overall survival of patients at the end of the study was as follows: 4 (21.05%) patients were alive, 7 (36.84%) had died, and 8 (42.11%) were lost to follow-up.

Toxicity

Only two serious adverse events were recorded during the study: one patient experienced diarrhea and one patient developed respiratory infection; the most frequently reported adverse events during the study were anemia (N=9), neutropenia (N=3), thrombocytopenia (N=9) and increased level of total bilirubin (N=3). Only 2 patients experienced rash of moderate intensity during treatment (Table 5).

Table 5. Adverse events

Adverse events	*Patients, N*				
	Mild	*Moderate*	*Severe*	*Total*	*Serious*
Diarrhea	-	1	1	2	1
Fatigue	-	1	-	1	-
Loss of appetite	-	1	-	1	-
Increased total bilirubin	2	1	-	3	-
Anemia	6	2	1	9	-
Leukopenia	1	-	-	1	-
Neutropenia	2	1	-	3	-
Thrombocytopenia	2	6	1	9	-
Rash	-	2	-	2	-
Pulmonary infection	-	-	1	1	1

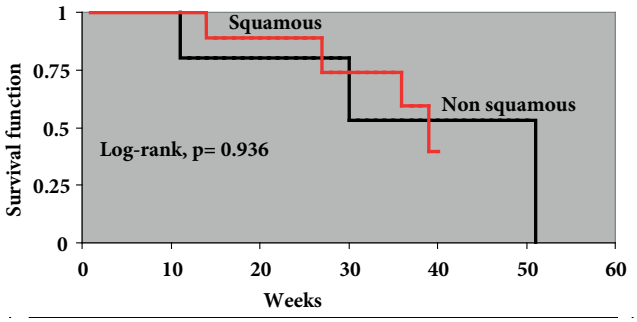

Figure 3. Overall survival of adenocarcinoma, bronchoalveolar carcinoma and large cell carcinoma (N=12 patients) vs squamous cell carcinoma (N=7 patients).

— Squamous cell carcinoma
— Adenocarcinoma & Bronchoalveolar carcinoma & Large cell carcinoma

Discussion

This study tried to confirm some trends recorded in previous studies which presumed a better response to chemotherapy associated with tyrosine kinase inhibitors (TKIs) for patients with advanced NSCLC vs chemotherapy alone. From basic research data exist which confirm that in NSCLC xenografts with similar levels of EGFR expression, the antitumor activity of erlotinib is robust both as monotherapy and in combination with chemotherapy [5].

The TRIBUTE study revealed that never smokers seem to have a longer survival than smokers when they received chemotherapy plus erlotinib vs chemotherapy alone in front-line treatment [6]. On the other hand, the BR21 study has demonstrated that erlotinib is effective and could prolong survival as second-line treatment for patients with advanced NSCLC with any histology and without taking into consideration the EGFR mutation status [7]. This behavior of NSCLC to erlotinib in second-line could preclude that chemotherapy which was administered

as first-line to patients in the BR21 study determined the sensitivity to erlotinib. Recently Pennel [8] reported inability to establish rules for administering combinations of TKIs and chemotherapy in NSCLC patients.

Kalikaki et al. [9] demonstrated that EGFR and K-RAS mutations (which can be found in 8.2 and 22.6% of NSCLC) have a predictive role for response in front-line chemotherapy (these results were published after the start of our study). These authors stated that EGFR mutation is a prognostic factor for response to chemotherapy and survival, is more frequently found in adenocarcinoma and is not associated with response to chemotherapy.

Because we lacked genetic information at the beginning of the study, predictability of response to erlotinib was based on the clinical patient characteristics. Despite the fact that mutation of EGFR and K-RAS has no clinical or pathological characteristics, EGFR mutation could be correlated with histopathology [9]. In this respect our results confirm that smokers had a shorter overall survival than the whole patient group (comparison with nonsmokers was not performed because of small number of this subgroup) and adenocarcinoma which is associated with an increased percentage of EGFR mutation was recorded in higher numbers than in squamous cell carcinoma and this had an impact on the response to erlotinib.

Patients with poor performance status (ECOG PS 2) show lower tolerability to chemotherapy and shorter survival compared with patients with good performance status. In the retrospective evaluation of ECOG 1594 study [10], the authors reported that toxicity to chemotherapy in patients with ECOG PS 2 was higher compared to patients with ECOG PS 0-1. A similar conclusion was reported in the CALGB 9730 trial and MILES trial (quoted by Devlin [10]).

A phase II study evaluated gemcitabine 1250 mg/m^2 plus carboplatin AUC 3 vs gemcitabine as monotherapy in NSCLC patients. Median overall survival was 4.8 and 6.7 months with 17.8 and 20% 1-year overall survival, respectively. These differences were without statistical significance. Grade 3–4 neutropenia, thrombocytopenia and anemia were significantly more frequent in the combination chemotherapy arm. The authors concluded that gemcitabine/carboplatin combination was not superior to gemcitabine alone in terms of clinical benefit (median time to progression and overall survival), while the combination was significantly more toxic [11].

In general, authors of studies with patients with advanced NSCLC with poor PS conclude that PS is the most important prognostic factor for survival and tolerability to chemotherapy. In patients with poor PS single-agent chemotherapy or a TKI are recommended in order to obtain a clinical benefit or symptom palliation [12-14].

Improvement in quality of life and a clinical benefit of patients with advanced NSCLC was reported in another study with single-agent chemotherapy (taxanes), especially in those where gemcitabine was used [15].

In a metaanalysis performed by Di Maio et al, in trials with second-line single-agent chemotherapy of advanced NSCLC overall survival was 37.3 weeks, which is comparable with our data but for patients with good PS [16].

Our results showed that the use of gemcitabine plus erlotinib in the treatment of patients with advanced NSCLC and poor performance status is a feasible option. The response rate of 15.8% and clinical benefit rate of 36.84% are, in our opinion, substantial. Such results were obtained also in monochemotherapy without TKIs but for patients with ECOG PS 0-1. The fact that gemcitabine could overcome the acquired resistance to erlotinib presumed in our study was confirmed in pancreatic cancer by Bartholomeusz et al. [17] and in NSCLC by Kuo et al. [18]. A phase III study will be necessary to clarify the value of erlotinib plus gemcitabine combination in the treatment of advanced NSCLC with ECOG PS 2.

Conflicts of interest

Drs. A.C. Grigorescu and C. Bala indicated financial funding by Roche Romania.

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