Retrospective Analysis of Clinical Efficacy of Erlotinib in Patients with Non-Small Cell Lung Cancer

Küçük Hücreli Dışı Akciğer Kanserli Hastalarda Erlotinibin Klinik Etkinliğinin Retrospektif Analizi

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Özet

Amaç: Bu çalışmada, ileri evre küçük hücreli dışı akciğer kanseri (KHDAK) olan Türk hastalarda, ikinci, üçüncü ve dördüncü seçim olarak uygulanan erlotinibin etkinlik ve güvenilirliğinin değerlendirilmesi amaçlandı. Gereç ve Yöntem: Daha önce tedavi görmüş, ileri evre KHDAK olan ve hastalık progresyonuna veya tolere edilemeyen bir yan etki oluşana kadar, oral yoldan günde 150 mg erlotinib alan 39 hasta retrospektif olarak analiz edildi. Bulgular: Tam yanıt gözlenmezken, 7 (%17.9) hastada kısmi yanıt ve 16 (%41) hastada stabil hastalık tespit edildi. Ortalama progresyonsuz sağkalım süresi 242 gün (%95 CI 51-224) ve ortalama genel sağkalım süresi ise 377 gündü (%95 CI 291-462). Genel sağkalım süresi kadınlarda erkeklere oranla anlamlı düzeyde daha uzundu (470 vs. 271 gün, p=0.046). Tedavi genel olarak iyi tolere edildi. En sık gözlenen yan etki cilt döküntüsü idi (%41). Tartışma: Erlotinib daha önce standart kemoterapi almış ileri evre KHDAK olan Türk hastaların tedavisinde güvelinilir ve etkili bulundu.

Anahtar Kelimeler

Erlotinib; Küçük Hücreli Dışı Akciğer Kanseri; Hedefe Yönelik Tedavi

Abstract

Aim: In this study, we aimed to evaluate the efficacy and safety of erlotinib as second-, third-, and fourth-line treatment for Turkish patients with advanced non-small cell lung cancer (NSCLC). Material and Method: Thirty-nine patients with advanced, previously treated NSCLC who received 150 mg of erlotinib once daily orally until disease progression or intolerable toxicity were retrospectively analyzed. Results: We observed no complete response, partial responses were observed in 7 (17.9%) patients, and 16 (41%) patients had stable disease. The median progression-free survival was 242 days (95% CI 51-224), and the median overall survival (OS) was 377 days (95% CI 291-462). The median OS of females was significantly better than male patients (470 vs. 271 days, p=0.046). The treatment was generally well tolerated. The most common side effect was skin rash (41%). Discussion: Erlotinib was safe and effective in treating Turkish patients with advanced NSCLC who had been previously treated with the standard chemotherapy.

Keywords

Erlotinib; Non-Small Cell Lung Cancer; Targeted Therapy

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Introduction

Non-small cell lung cancer (NSCLC) is the most frequent cause of cancer death in the world [1]. Although surgical resection is the only potentially curable treatment for this malignancy, most patients with NSCLC present with advanced disease requiring systemic chemotherapy [1, 2]. The current standard therapy for patients with advanced disease is platinum-based double-agent chemotherapy. Chemotherapy, however, does not substantially change the long-term outcome for most NSCLC patients, and is administered with palliative intent, in order to control symptoms, to prolong life, and to improve quality of life [1, 2].

Over the last few years, with the advancements of new molecular techniques and better understanding of biological events implicated in carcinogenesis, significant progress has been achieved in the treatment of patients with advanced NSCLC or other solid tumors [3]. The introduction of molecularly targeted agents in the therapeutic armamentarium has provided new options for the treatment of NSCLC patients. The epidermal growth factor receptor (EGFR) has been shown to play an important role in the development and progression of NSCLC [4]. The EGFR is a member of the ErbB tyrosine kinases family of cell membrane receptors that are important mediators of cell growth, differentiation, and survival [4, 5]. Therefore, targeting the EGFR represents a promising molecular approach in this malignancy. In recent years the two small molecules, erlotinib and gefitinib, have been developed and extensively studied in patients with NSCLC [4-6]. Both drugs are orally available small molecules that selectively and reversibly inhibit the tyrosine kinase domain of EGFR [4-6].

Erlotinib has been demonstrated to feasible and effective in advanced NSCLC patients progressing after first-line or second-line chemotherapy [7]. A recent double-blind, placebo-controlled phase 3 study comparing erlotinib with placebo in previously treated patients with stage IIIB/IV NSCLC (BR.21 trial) reported the first evidence of an EGFR inhibitor prolonging survival in chemotherapy-refractory NSCLC [8]. Patients receiving erlotinib demonstrated significantly longer overall survival (6.7 months vs. 4.7 months; $P < 0.001$) and progression free survival (2.2 months vs. 1.8 months) then those receiving placebo. The overall erlotinib response rate was 8.9%. On the other hand, the efficacy of erlotinib has not been well studied in Turkey. In this study, we aimed to evaluate the efficacy and safety of erlotinib as second-, third-, and fourth-line treatment of NSCLC.

Material and Method

We conducted a retrospective medical record review of 39 patients with advanced NSCLC treated with erlotinib at our hospital between January 2009 and July 2012. All patients had received at least one prior chemotherapy regimen before the administration of erlotinib treatment. All patients received 150 mg of erlotinib once daily orally until the occurrence of progressive disease or unacceptable toxicity. The medical records of enrolled patients were reviewed to collect demographic, clinical, and pathology data. Treatment history, clinical outcomes, and treatment-related toxicities were extracted from the medical records. Patients were seen regularly during the treatment period by their medical oncologists and underwent physical examinations and laboratory testing, including complete blood cell counts and a chemistry panel. Treatment response was evaluated using the appropriate imaging modalities every 2-3 months. Progression-free survival (PFS) was measured from the first day of erlotinib treatment until radiological or clinical disease progression. Overall survival (OS) was calculated from the first day of erlotinib treatment to patient death or the last date of follow-up. The Kaplan-Meier method was used to estimate the survival times. Differences in patient characteristics were assessed with the chi-square test. Objective response rate (ORR) was defined as the proportion of patients with the best response of either a complete or partial response. The Institutional Review Board at our university approved the study protocol before the clinical records were accessed (No: 2012-4/6).

Results

There were 21 males and 18 females (median age: 58 yrs, range 28-78). Demographic data and the clinicopathologic characteristics of the patients are summarized in Table 1. Most patients had a performance status of 0 or 1 (64%), and 84.6% of patients had adenocarcinoma. All patients had received platinum-based doublet regimens as the first-line treatment. Sixteen (41%) patients received erlotinib as second-line, 19 (48.7%) patients as third-line, and four (10%) patients as fourth-line therapy. Thirty-six (92%) patients had never smoked, and 3 patients were ex-light smoker. EGFR mutation status was unknown in all patients. The median duration of erlotinib treatment was 158 days (range 30-600). There was no complete response (CR) to erlotinib. Seven (17.9%) patients achieved a partial response (PR) and 16 (41%) patients experienced stable disease (SD). The overall ORR was 17.9%. The median PFS was 242 days (95% CI 51-224), and the median OS was 377 days (95% CI 291-462) (Figure 1, 2). Although there was no PFS difference between male and female patients, the median OS of females was significantly better than male patients (470 vs. 271 days, p=0.046).

Table 1. Patient's demograhic and clinicopathologic characteristics (n=39)

Characteristics	n (%)
Gender	
Male	21 (53.8)
Female	18 (46.2)
ECOG PS	
0	10 (25.6)
1	15 (38.4)
2	13 (33.3)
3	1 (2.6)
Histologic type	
Adenocarcinoma	33 (84.6)
Bronchoalveolar carcinoma	6 (15.4)
Tumor stage	
III	4 (10.3)
IV	35 (89.7)
Erlotinib treatment	
Second-line	16 (41)
Third-line	19 (48.7)
Fourth-line	4 (10)

ECOG PS= Eastern Cooperative Oncology Group performance status

Erlotinib treatment was generally well tolerated. The most common side effect was skin rash (41%) (Table 2). Mucositis (20.5%), stomatitis (12.8%), and diarrhea (15.4%) were the other common side effects. No patient discontinued treatment due to adverse events. However, erlotinib dose was reduced from 150 to 100 mg/day in 10 (25.6%) patients because of adverse

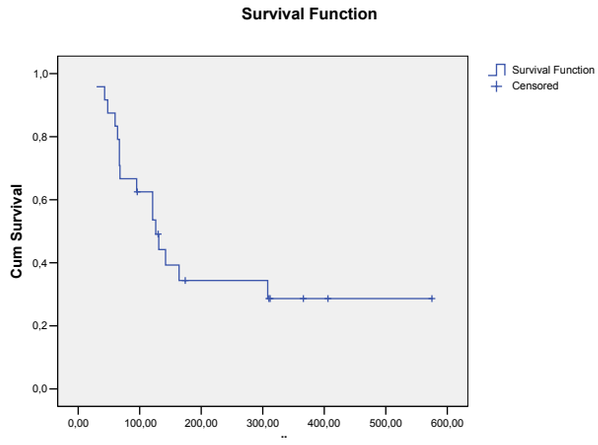


Figure 1. Progression-free survival of the patients treated with erlotinib

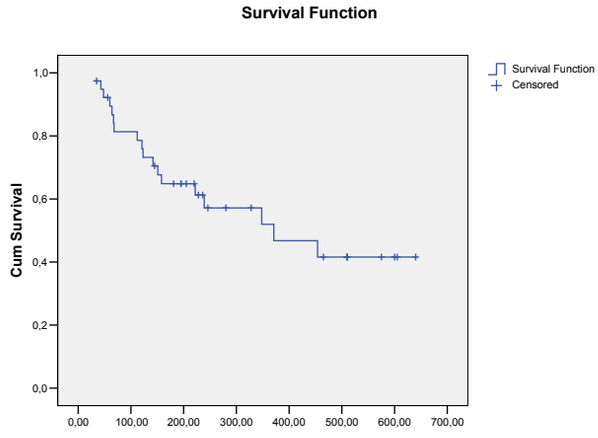


Figure 2. Overall survival of the patients treated with erlotinib

Table 2. Worst toxicity per patient according to WHO toxicity criteria

Type	Grade ½ n (%)	Grade ¾ n (%)
Skin rash	10 (25.6)	12 (30.7)
Mucositis	8 (20.5)	0
Stomatitis	5 (12.8)	0
Diarrhea	6 (15.3)	0

WHO= World Health Organization.

Table 3. Summary of clinical studies investigating efficacy of erlotinib in Turkish patients with advanced non-small cell lung cancer

Study	No of patients	OR (%)	PFS	OS	Line of Treatment (%)
Karaca et al [11]	80	14	12 months	18 months	2. (62.5) ≥3. (37.5)
Aydıner et al [15]	109	15	4.2 months	8.5 months	2. (56) ≥3. (44)
Present study	39	17.9	242 days	377 days	2. (42) ≥3. (58)

No= number, OR= Overall response rate, PFS= Progression-free survival, OS= Overall survival

events. The toxicities were manageable after dose reduction of erlotinib.

Discussion

Erlotinib and other novel targeted agents have been gradually introduced in the clinical management of NSCLC as a new generation of cytostatic drugs [9]. These agents represent a promising treatment option in patients with chemorefractory disease. Erlotinib has been widely used in advanced NSCLC since its initial approval in 2005 [10]. It inhibits the cascade of events induced by EGFR activation, including apoptosis, metastasis development, and proliferation. Erlotinib is currently the only one EGFR tyrosine kinase inhibitor approved for use as the subsequent line of chemotherapy after failure of the first and other line platinum-based regimen [9, 10].

The results of this retrospective study show that erlotinib monotherapy is active and relatively well-tolerated in Turkish patients with advanced NSCLC who progressed after first-line chemotherapy. Seven (17.9%) patients partially responded to erlotinib and 16 (41%) patients showed stable disease. Therefore, we were able to achieve a 58.9% disease control rate (ORR + SD). Side effects were predictable and manageable, similar to those seen in previous erlotinib clinical trials [8, 11-15]. The median PFS and OS of the study population were 242 and 377 days, respectively, which were similar to those reported in other similar studies [8, 11-15].

The efficacy and safety of erlotinib have not been adequately evaluated in Turkish patients. To the best of our knowledge, only two previous studies have investigated the efficacy of this agent in a Turkish population with previously treated advanced NSCLC (Table 3). Karaca et al [11] performed a multicenter retrospective study on the efficacy and safety of erlotinib in 80 advanced NSCLC patients. With an overall disease control rate of 40%, they reported that one patient had achieved CR, 10 patients had PR, and 21 patients had SD [11]. The most common adverse effects reported were skin rash (56%), diarrhea (9%), and anorexia (8%). The authors have reported median PFS was 12 months, and median OS was 18 months. In another retrospective study, Aydıner et al [15] reviewed 109 patients with advanced NSCLC who had previously failed at least one line of chemotherapy and received subsequent erlotinib (150 mg/day orally). The disease control rate was 55%, including CR (2%), PR (13%), and SD (40%). The median PFS and OS were 4.2 and 8.5 months, respectively. A multivariate analysis of initial prognostic factors revealed that ECOG PS ≥2, presence of intra-abdominal metastasis, 2 or more prior chemotherapy regimens, and weight loss >5% were independent adverse prognostic factors for OS.

Although erlotinib is active in unselected patients, it has been shown that some patient subpopulations might derive greater benefit from erlotinib than others. Some clinical features, including female sex, Asian ethnicity, never having smoked, and adenocarcinoma are known to be associated with the presence of an activating EGFR mutation and have been significantly associated with responsiveness to erlotinib [3-10]. It has been suggested that EGFR mutations occur almost exclusively in adenocarcinomas [16], and patients with squamous cell carcinoma (SCC) have not been considered ideal candidates for treatment with erlotinib [10]. A study on 95 resected pure SCC patients revealed that EGFR mutations are usually absent [17]. Karaca et al [11] detected that female patients had a marginally better disease control rate with erlotinib compared to male patients (49% vs 27%, p=0.052). They also found that female patients had significantly longer median PFS than male patients (18 vs 5 months, p=0.03). In our study, although there was no PFS difference between male and female patients, the median OS of females was significantly better than male patients (470 vs. 271 days, p=0.046). It was shown that the EGFR mutation rate in females is significantly higher than that of males [3-10].

Therefore, better outcome for women compared with men in these studies may be explained by the presence of higher rates of EGFR mutations. However, none of our patients were tested for EGFR mutations. In the study of Aydıner et al [15], EGFR mutation status was available for 65 patients, and patients with EGFR mutation showed a trend toward better survival (p=0.06) compared with patients with wild-type EGFR.

Our study has some limitations. The primary limitation of this study was that it was a retrospective review. Due to the nature of retrospective reviews, required information may be incomplete or absent. The study also includes a relatively small number of patients from a single institution. Therefore, we could not examine the effects of potential prognostic factors on the outcome. On the other hand, our study gives some specific messages to clinicians. Turkish patients with advanced NSCLC might derive a clinical benefit from erlotinib and can tolerate this agent well. Erlotinib may be beneficial for advanced NSCLC patients with unknown tumor EGFR mutation status, and such patients should not be excluded from this treatment option.

In conclusion, the present study suggests that single-agent erlotinib is active and well-tolerated therapy for unselected patients with advanced NSCLC progressing after the standard chemotherapy.

Competing interests

The authors declare that they have no competing interests.

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