RESEARCH ARTICLE

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Clinical Effectiveness of Erlova in *EGFR*-Mutated Non-Small Cell Lung Cancer: An Affordable Price with Clinical Benefit

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Abstract

Background: Thyrosin kinase inhibitors (TKIs) is approved for the first line treatment of non-small cell lung cancer (NSCLC) patients with epidermal growth factor receptor (*EGFR*) mutation. This study performed to assess clinical effectiveness and safety of Erlova (generic form of Erlotinib). **Methods:** Somatic mutations of *EGFR* gene were studied in tumor tissue by polymerase chain reaction (PCR) and bi-directional sequencing in 513 chemonaive and histologically verified lung adenocarcinoma Iranian patients. Patients with *EGFR* mutation received Erlova at 150 mg/day as first line treatment. Primary endpoint was progression free survival (PFS). **Results:** About 21% (n=109) cases had *EGFR* mutation. Most *EGFR* mutations were occurred at exon 19. Among them, sixty nine patients treated with Erlova. Median PFS was 11.4 months and objective response rate (ORR) was about 88%. Most frequent treatment related adverse events was skin rash. **Conclusion:** Our findings showed Erlova had remarkable effectiveness. In mutation-positive patients with *EGFR*, Erlova can be used safely instead of other tyrosine-kinase inhibitors.

Keywords: Carcinoma- non-small-cell lung- safety- Erlotinib Hydrochloride

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Introduction

Lung cancer is the most leading cause of cancer-related death worldwide (Bray et al., 2018). In Iran, it is the forth and second common cancer and, cause of cancer mortality in both sexes, respectively (Mosavi et al., 2009).

Non-small cell lung cancer (NSCLC) often diagnosed at advanced stages of the disease. Old cytotoxic chemotherapy do not have pomissing results in term of response rate or survival. Recently, outcome of NSCLC patients has been greatly improved by new treatment options such as targeted therapy and immunotherapy (Proto et al., 2019). This new treatment implicated in presense of definite genetics alternations such as Kirsten ras (KRAS), anaplastic lymphoma kinase (ALK), repressor of silencing 1 (ROS1) and programmed death-ligand 1 (PDL-1) which have been studied to date. The most prevalent mutations tend to occur is the Epidermal Growth Factor Receptor (*EGFR*) mutation. *EGFR* is a transmembrane protein binding to "epidermal growth factor"(EGF) and has a tyrosine kinase domain located in exons 18-24. Thyrosine kinase inhibitors(TKIs) target the kinase domain of *EGFR* and make to achive favorable primary clinical responses in practice (Buonerba et al., 2019) especially in Adenocarcinoma subtype of NSCLC. Erlotinib belongs to the first generation of TKIs which reversibly bind to *EGFR*. For many years, in Iran use of Erlotinib was limited due to the high drug as well *EGFR* testing cost. Recently, generic form of this agent as "Erlova"(manufactured by Osveh company) has been released in Iran market.

This study collected data on frequency, treatment response and outcome in patients harboring *EGFR* mutation and treating with Erlova. Also, the clinical effectiveness and safety of Erlova were assessed to provide an insight for the future direction of rational treatment decisions.

Materials and Methods

From Sep 2014 to Jun 2019, five hundered and thirteen chemo-naive patients (no previous history of chemotherapy, immunotherapy, or biologic agents) were eligible for this prospective, unicenter, open-label, non-randomized and single-arm study at National Institute of Tuberculosis and Lung Disease (NRITLD), Masih Daneshvari Hospital.

Mutation detection

Deoxyribonucleic acid (DNA) was isolated from the

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tumor sample paraffin block from the surgical specimens, fine needle biopsies and pleural effusions. It was quantified and amplified by Nested Polymerase Chain Reaction (nested-PCR) using primers for exons 18-21 of *EGFR*. The tumor samples for *EGFR* mutation detection consisted of at least five unstained 10-µm sections mounted on a non-charged microscope slide containing at least 20% tumor tissue. PCR products were sequenced with application binary interface (ABI) 3500xl DNA Sequencer and analyzed bi-directionally.

Eligibility criteria

The patients with histologically confirmed Adenocarcinoma, stages IIIB and IV (by AJCC, 8th edition) (Rami-Porta et al., 2014) is primarily tested for *EGFR* mutation. Patients with mutated *EGFR* gene were enrolled in this study. Other eligibility criteria included the following: age ≥ 18 years old, at least one unidimensionally measurable or assessable disease, adequate bone marrow reserve, serum creatinine less than or equal to 1.5 mg/dL or a calculated creatinine clearance greater than or equal to 60 mL/min, bilirubin level less than or equal to 2.0 mg/dL, aspartate transaminase (AST) less than or equal to twice the institutional upper limits of normal, or less than or equal to four times the institutional upper limits of normal if the patient had liver metastasis. Neither of patients had prior chemotherapy.

Eligible patients assigned to receive Erlova (manufactured by Osveh.,) 150 mg daily up to disease progression (according to criteria of Jackman et al) (Jackman et al., 20010) or unacceptable toxicity. Clinial effectiveness of Erlova parameters included disease assessments by computed tomography(CT) scans within 30 days prior to the first dose of study drugs and then every 8 weeks thereafter. Response rate was evaluated according to "Response Evaluation Criteria in Solid Tumors" (RECIST) criteria (Green and Weiss., 1992). Objective response rate (ORR) defined as the sum of the number of complete response (CRs) and partial response (PRs).

Dose modification was allowed during treatment course according to the encountered toxicity. Toxicity assessment was based on "Common Terminology Criteria for Adverse Events" (CTCAE) version 3.0 (Common Terminology Criteria for Adverse Events., 2003). We treated skin toxicities related to Erlova according to the recommendations with corticosteroid cream or antibiotic gel. Loperamide for diarrhea and topical eye gel or drops for the keratoconjunctivitis sicca managements were administrated. Criteria for withdrawal from study were unacceptable toxicity as determined by the treating physician in consultation with the study coordinator, a delay in treatment greater than 2 weeks, requirement for palliative radiotherapy, or patient refusal.

Statistical analysis

The primary end point of study was Progression free survival (PFS). Secondary objective was adverse events.

The mean ± standard deviation (SD) was calculated for continuous variable. All confidence intervals (CIs) for parameters to be estimated were constructed with a significance level of alpha=0.05 (a 95% confidence level). Kaplan Meier's survival curves were obtained for PFS. PFS was calculated from date of registration in study to date of progression or death. Patients who were alive or lost of follow up at time of data analysis, censored for PFS analysis.

The analysis included all patients who received at least one dose of assigned treatment. A P-value of less than 0.05 was considered statistically significant. IBM SPSS statistical software version 19 for Windows (IBM, Armond, NY, USA) was used for data analysis.

Results

A total of 513 Adenocarcinoma patients were assigned to test *EGFR* Mutation at time of disease diagnosis. In 109 (21.2%) paraffin block *EGFR* mutation was documented and in rest of them (n=404) mutation was not seen. Among positive *EGFR* mutation cases, 40 patients had no consensus for treatment, thus 69 cases treated with Erlova. Study outcomes and endpoints survival data analysis was performed only for patients who received Erlova as first-line chemotherapy.

Mean age of patients who treated with Erlova were

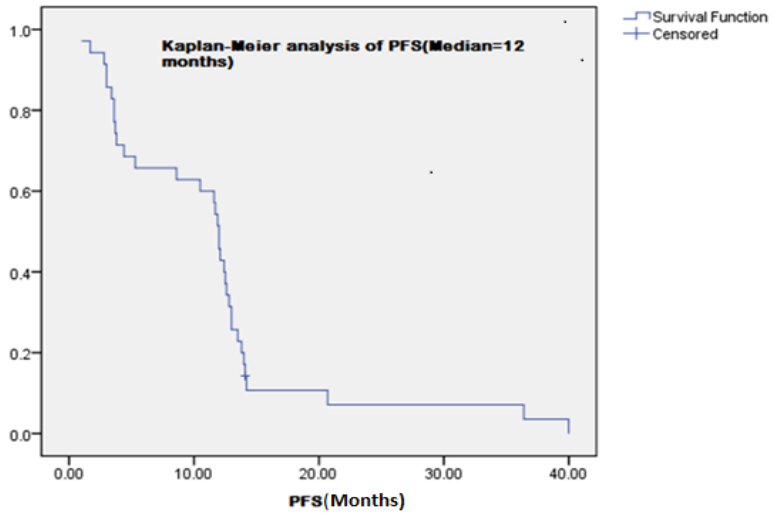

Figure 1. The Kaplan-Meier Survival Curve from Progression Free Survival (PFS) in the Study Population

Table 1. Baseline Patient and Disease Characteristics of Study

Column 1	Column 2
Age(Mean±SD a, range)	(61.1±12.02, range:29-89)
Sex	Male: n=26 (37.7%)
	Female: n=53 (62.3%)
Stage b	IIIB: n=1 (1.4%)
	IV: n= 68 (98.6%)
Mutated Exon	Exon 18: n=2 (2.9%)
	Exon 19: n= 51 (73.9%)
	Exon 21: n=13 (18.8%)
	Exon19,21:n=1 (1.4%)
	Exon 19, 18: n=1 (1.4%)
	Exon 18, 21: n=1 (1.4%)

A, standard deviation; b, staging was done according to AJCC, 8th edition

61.1 years. Female/ male ratio was 1.4. Median duration of follow-up was 11.9 months (range: 1-61.3 months). Patient and disease baseline characteristics were shown in Table 1.

Survival outcome

During the follow-up, 34 (31.8%) of patients had documented disease progression. The mean PFS was 11.4±.1.5 months (Figure 1). Also, at time of data analysis, 14 (13.3%) of study group, had expired.

Treatment effectiveness

Of the 69 patients treated with Erlova, 66 were assessable for response evaluation. The lost of follow up after first course of therapy was reason of not response assessing. ORR and disease control rate were 61 (87.3%) and 64(95.1%), respectively. In 2 cases (2.8%)-after first assessment for response-progressive disease was documented.

Safety

In all patients, Erlova was well tolerated and demonstrated a consistent safety and toxicity profiles were compatible with the expectation. Main toxicities and adverse events were shown in Table 2. Skin rash with incidence of 76.8% was the most common adverse events in our study. Severe skin rash led to dose adjustment and discontinuation of Erlova in 2 and one patient, respectively. No death was found related to the study medication.

Discussion

Medicine's access especially in cancer field varies from country to another, and many patients in low and middle income countries, are not able to access many therapies which be needed. Nevertheless for many years, in our country, first line chemotherapy with Erlotinib was very limited because it was not affordable for a large number of patients. As we know, this study is the first investigation, focused on Iranian patients population who treated with generic drug" Erlova by Osveh" as first line

Table 2. CTCAE Grade 1 or 2 vs Grade 3 or 4 Toxicities, Safety Population

Column 1	Column 2	Column 3
Toxicity	CTCAE a Grade	CTCAE Grade
	1 or 2 n (%)	3 or 4 n (%)
Rash	45 (65.1)	8 (11.5)
Diarrhea	3 (2.9)	
Nephrotoxicity	2 (1.9)	
Thrombocytopenia	-	-
Neutropenia	-	-
Anemia	1 (1)	-
Sensory neuropathy	-	-
Alopecia	-	-
Mucositis	-	-
Vomating	-	-
Constipation	-	-
Interstitial lung disease	-	-
Keratoconjunctivitis sicca	2(2.8)	

a CTCAE, common toxicity criteria for adverse events.

chemotherapy. In regard to the median PFS and ORR of this protocol with a generic drug, this study successfully met its primary and secondary end-points. Importantly, this regimen exhibited an acceptable toxicity and a well-tolerated safety profile of Erlova, too.

EGFR mutations incidence in NSCLC, ranges from ~15% in Caucasians to 47%-64% % in East Asians (Pao and Girard., 2011; Basi et al., 2017). In our study, the number of *EGFR* mutation is more near to Caucasians and a few numbers of studies in Asians such as India and Japan (Chougule et al., 2013). These frequency differences might be related to the ethnicity, difference in PCR steps, the method of mutation detection and the software which is used for analyzing the sequences, and also, the sequencer system (Lam et al., 2004).

First-line treatment with TKIs for patients with advanced NSCLC harboring activating *EGFR* mutations, led to response rates of 56 to 83% (Lin et al., 2016; Rosell et al., 2012). The ORR in our study is in accordance with studies from East-Asia which response rates were reported from70 to 75% (Douillard et al., 2014) and Zhou et al., (2011) study with 80.3% ORR.

We chose PFS as main endpoint because that would be a valid surrogate endpoint, unaffected by the use of second-line therapy and can be assessed much sooner. The median PFS of 10 to 14 months observed in treatment with Erlotinib (Lin et al., 2016). Of note, median PFS in our cohort is in the range of mentiend study and is partly similar to other studies with Erlotinib (12.3 months in Cappuzzo et al., (2010) and 12.8 months in Markóczy et al., (2018). Shorter PFS than our result have been reported by Spigel et al., (2103) and Rossell et al., (2012).The high ORR and PFS of our cohort may be related to higher *EGFR* mutation rate at exon 19, high percentage of non smoker patients and homogeneity of NSCLC subtype.

Erlova was generally well tolerated in our study. There were no unexpected safety findings relating to Erlova in this study. Most of adverse events were generally mild to

moderate. The most common reason for Erlova-related dose reductions or discontinuations was rash that is a well-known adverse event of TKIs. According to other studies, the safety profile of Erlotinib has been established in more than 9,000 patients in clinical trials and expanded access programs (Groen et al.,2008). Most commonly adverse events in mentioned studies were generally mild and manageable diarrhea and skin rash, as we observed.

The study conclusions must be tempered by the limitations such as the non-placebo controlled or comparing with main Erlotinib brand and single-arm study design.

In conclusion, the Erlova exhibited favorable efficacy in patients with advanced stage NSCLC. Therefore, Erlova is a suitable candidate as first-line treatment for NSCLC instead of other high cost TKIs.

Author Contribution Statement

The authors confirm contribution to the paper as follows: study conception and design: Sharareh Seifi; Adnan Khosravi and Ramin Radmanesh; data collection: Zahra Esfahani-Monfared; analysis and interpretation of results: Zahra Esfahani-Monfared; draft manuscript preparation: Sharareh Seifi ;Adnan Khosravi; Babak Salimi; Zahra Esfahani-Monfared; Saeed Yaghoubifard, SaraTalebianpour. All authors reviewed the results and approved the final version of the manuscript.

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The study was approved by Shahid Beheshti Medical University's ethics and scientific committees (number: IR.SBMU.REC.1394.196) and was conducted in compliance with the Helsinki Declaration and Good Clinical Practice guidelines (GCP). Informed consent was obtained from each participant before they participate in the study. The authors received no financial support for the research, authorship, and/or publication of this article.

Conflicts of Interest

There is no conflict of interests.

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