ORIGINAL ARTICLE

Concurrent radiotherapy and chemotherapy with erlotinib followed by maintenance erlotinib in patients with Epidermal Growth Factor Receptor mutation- positive adenocarcinoma lung

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Abstract

Objective: To assess the efficacy and tolerability of erlotinib in combination with radiation therapy followed by maintenance therapy in Stage III and IV, epidermal growth factor receptor mutation-positive adenocarcinoma lung patients.

Methods: The single-arm, quasi-experimental study was conducted at the Mayo Hospital, Lahore, Pakistan, from September 2013 to December 2014, and comprised patients with lung adenocarcinoma who were followed up till December 2017. The patients received concurrent radiation therapy (60-70 Gy in 30-35 fractions) along with erlotinib 150mg/day, followed by erlotinib 150mg/day as maintenance therapy till disease progression. Primary endpoint was overall response rate according to Response Evaluation Criteria in Solid Tumours guideline version 1.0, while secondary endpoint was progression-free survival, overall survival and toxicity assessment with Common Terminology Criteria for Adverse Eventsversion 3.0. Before starting erlotinib, all patients received four cycles of standard chemotherapy with platinum doublets (Pemetrexed, Docetaxel, Paclitaxel, Gemcitabine). Data was analysed using SPSS 16.

Results: of the 62 patients initially enrolled, 49(79%) completed the study. Of them, 37(75.5%) patients were smokers. Mean age of the patients was 57.0±8.51 years (range: 31-73 years) and 40 (81.6%) were male subjects. Objective response rate was 71.4% (n=35). Median progression-free survival for stage III disease was 7.4 months and for stage IV disease 2.8 months. Corresponding median overall survival rates were 12.9 months and 5.5 months. Common adverse events observed were rash n=30(61.2%), fatigue n=21(42.9%) and diarrhoea n=18(36.7%).

Conclusion: Concurrent radiotherapy with erlotinib was effective and well-tolerated in patients with locally advanced adenocarcinoma lung harbouring epidermal growth factor receptor mutation.

Keywords: Adenocarcinoma lung, EGFR mutation, Concurrent radiotherapy, Erlotinib, Non-small cell lung cancer, Targeted therapy. (JPMA 69: 1605; 2019). **doi: 10.5455/JPMA.297968.**

Introduction

Lung cancer is the most common cancer worlwide, causing death in one in five cases, and is the leading cause of cancer-related mortality.[1] Keeping in view the current trends, figures are even higher for developing countries.With the current treatment modalities, the 5-year survival rates for non-small cell lung cancer (NSCLC) range from 49% for stage IA to a mere 1% for stage IV.[2] Therefore, the need of the hour is to formulate new treatment approaches to combat the dismal survival rates.

NSCLC accounts for 80% of all lung cancers, out of which 32-40% comprises adenocarcinoma.[1] The epidermal growth factor receptor (EGFR), a member of the ErbB(protein) family of receptor tyrosine kinases, is over-expressed in about 41% of lung adenocarcinomas.[2] EGFR signalling cascade includes various major pathways of cell migration, adhesion and proliferation.[3] Over-expression of these is involved in tumour progression, angiogenesis, metastasis, resistance to radiotherapy and, thus, poor prognosis.[3] Increasing amount of attention is

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now being paid to incorporation of molecular targeted agents into current therapies, and more focus has been on EGFR signal transduction pathway in correlation with tumour microenvironment.

A number of preclinical researches have established synergistic anti-tumour activity of EGFR inhibitors and radiotherapy in vivo and in vitro.[3] Erlotinib is a small molecule, reversible inhibitor of EGFR, which has been tested in some clinical trials with improved prospects. Erlotinib enhances apoptosis induction, inhibits EGFR autophosphorylation and Rad51 (DNA repair protein) expression, and promotes radiation response at several levels, including cell cycle arrest, accelerated cellular repopulation, and deoxyribonucleic acid (DNA) damage repair.[4] It has proven to produce high response rates in previously untreated cases as well as extended survival when used as maintenance therapy after standard first-line platinum-based chemotherapy in advanced NSCLC.[5,6] Therefore, combining erlotinib with thoracic external beam radiotherapy has the potential to improve local tumour control in patients with unresectable NSCLC, based on theoretical promise that it inhibits EGFR, thereby increasing radio-sensitivity.

The current study was planned to assess efficacy and tolerability of erlotinib in combination with radiation therapy followed by maintenance therapy in Stage III and IV EGFR mutation-positive adenocarcinoma lung patients.

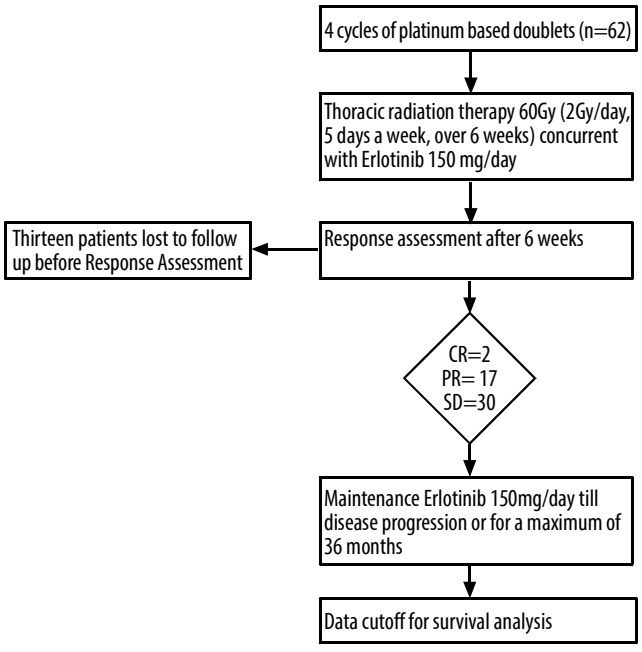
Patients and Methods

The quasi-experimental, phase-II single-arm trial was conducted at the Department of Oncology and Radiotherapy, Mayo Hospital, Lahore, Pakistan, from September 2013 to December 2014, while fFollow-up was done till December 2017. Approval was obtained from the institutional review board and the Advance Study and Research Board of the King Edward Medical University / Mayo Hospital, Lahore.

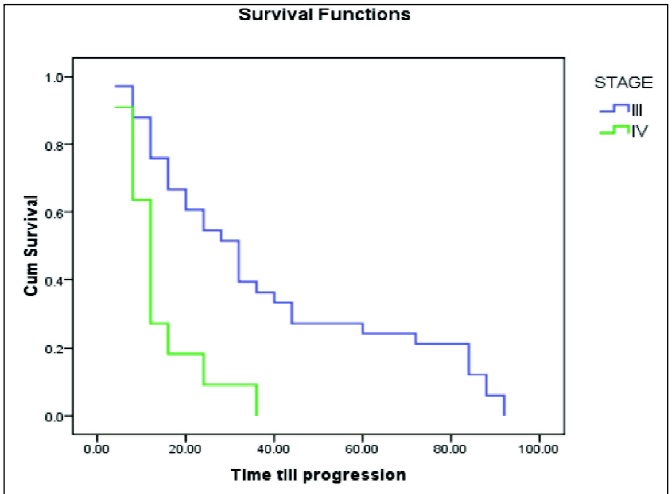
All patients diagnosed with lung adenocarcinoma were included after taking informed consent from each of them. Patients who did not give consent were excluded. The patients had histologically-confirmed adenocarcinoma, locally advanced tumour stage III A/B or IV (with local metastasis only) and unresectable or had medically inoperable disease. EGFR mutation was tested by real-time polymerase chain reaction (PCR) after DNA extraction from Formalin Fixed Paraffin Embedded Tissue (FFPE).

The primary endpoint was overall response rate (ORR), while secondary endpoints included progression-free survival (PFS, overall survival (OS), safety and tolerability. Complete pre-treatment evaluation was done. Patients received erlotinib (150mg / day) administered until objective progression of disease, intolerable toxicity or withdrawal from the study for other reasons. Response was evaluated 6 weeks after therapy using Response Evaluation Criteria in Solid Tumours (RECIST).[7] Patients with progressive disease at any stage were withdrawn from the study and treated as per institutional guidelines. Toxicities were graded using Common Toxicity Criteria for Adverse Events (CTCAE)[1] version 3.0. In case of grade III or IV toxicities, treatment was temporarily interrupted and restarted upon resolution. Patients on maintenance erlotinib therapy were followed with 4-weekly visits and 6-monthly computed tomography (CT) scans in asymptomatic patients till disease progression / death. Interval CT scans were also done in case of symptomatic patients. The follow-up data was used to construct PFS and OS curves using Kaplan-Meier method with 95% confidence interval (CI). Data was analysed using SPSS 16. ORR was determined on the basis of investigator data and summarised in the full analysis set with 95%

Annexure: Study Scheme.

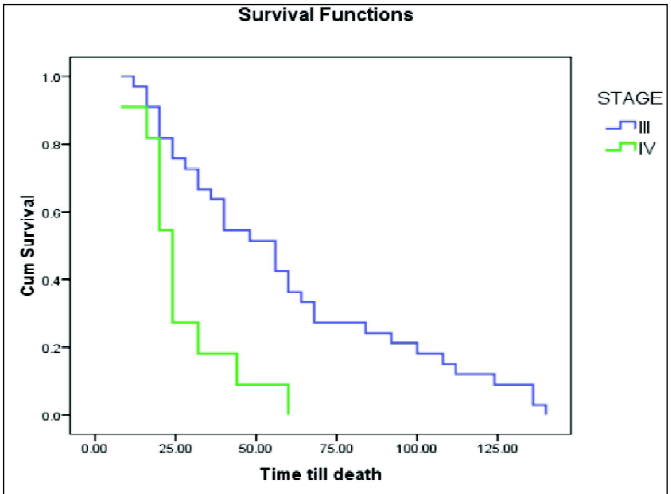


PR: Partial response, SD: Stable disease, PD: Progressive disease, CR: Complete response.



Median PFS for stage III was 32 weeks (7.4 months), 95% CI [22.569, 41.431]
Median PFS for stage IV was 12 weeks (2.8 months), 95% CI [9.105, 14.895]

Figure-1: Progression Free Survival (PFS).



Median OS for stage III was 56 weeks (12.9 months), 95% CI [40.101, 71.899]
Median OS for stage IV was 24 weeks (5.5 months), 95% CI [20.140, 27.860]

Figure-2: Overall Survival (OS)

Table: Epidemiology.

		Count	Percentage
Gender	Male	40	81.6
	Female	9	18.4
Age (in years)	31-40	2	4.1
	41-50	8	16.3
	51-60	21	42.9
	61-70	16	32.7
	71-80	2	4.1
Stage	III A	22	44.9
	III B	15	30.6
	IV	12	24.5
Smoking Status	Smoker	37	75.5
	Non-smoker	12	24.5
ECOG	0	10	20.4
	1	24	49.0
	2	15	30.6

ECOG: Eastern Cooperative Oncology Group.

CI. Safety analysis included incidence of adverse events, interruption in treatment and changes on physical examination or investigations.

Results

Of the 62 patients initially enrolled, 8(13%) experienced progressive disease during induction chemotherapy or concurrent radiotherapy, became so frail and cachectic that they were not able to take anything orally, and did not complete the protocol, while 5(8%) were lost to follow-up (Annexure). The study sample, as such, comprised 49(79%) patients. Of them, 40(82%) were males and 9(18%) were females. Overall mean age was 57±8.5 years (range: 31-73 years) (Table).Of the total, 6(12.2%) patients showed complete response (CR), 29(59.2%) partial response (PR), 10(20.4%) demonstrated stable disease and 4(8.2%) had progressive disease. Media PFS of the patients was noted (Figure 1). ORR was 71.4% (n=35) (95% CI: 2.02-2.46). Median PFS for stage III disease was 7.4 months (95% CI: 22.57-41.43) and for stage IV disease 2.8 months (95% CI: 9.1-14.89). Median OS 12.9 months (95% CI 40.10-71.89) and 5.5 months (95% CI 20.14-27.86) for stage III and stage IV disease respectively (Figure 2). OS ranged from 8 weeks to 140 weeks. Common adverse events were rash in 30 patients (61.2%), fatigue in 21 patients (42.9%) and diarrhoea (36.7%) in 18 patients.

Haematological toxicities in only 5 patients (10.2%) comprised of anaemia, neutropenia and thrombocytopenia. Others noted were nausea in 17 (34.70%) patients, anorexia in 12 (24.50%) patients and altered liver functions in 6 (12.20%) patients.

Discussion

The current study is the first of its kind in Pakistani population. Blockade of EGFR signalling has been shown to increase radio-sensitivity through three different mechanisms: by suppressing DNA repair, by reducing proliferation, and by inhibiting anti-apoptotic pathways.[9] It is also possible that radiotherapy enhances the effect of EGFR inhibitors by creating a hypoxic environment and cyto-reduction of tumour.[10] In addition, the principle

favouring combination of a local agent with systemic therapy for maximal effect is relevant to this approach.[11] Finally, toxicities associated with these two are generally, though not entirely, non-overlapping, enabling their concomitant use.[11]As for the optimal timing of administration of the two treatment modalities, several phase III randomised studies have shown a clear benefit of concurrent over sequential chemo-radiotherapy.[1] Erlotinib is a small molecule, reversible inhibitor of EGFR. Tarceva (erlotinib) was approved by the Food and Drug Administration (FDA) in November 2004 for the treatment of chemotherapy-resistant advanced NSCLC and, in April 2010, as maintenance therapy for patients whose disease had not progressed after four cycles of platinum-based chemotherapy.[12,13]

International data has shown that sequential administration of erlotinib following chemotherapy leads to a significant improvement in response rate in patients previously not responding to first-line chemotherapy regimens.[14] Similarly in this study, administration of concurrent erlotinib and radiotherapy led to CR in 6(12.2%) patients compared to just 2(3.2%) after standard platinum-based chemotherapy. A favourable outcome was seen with PR in 59.2% subjects with erlotinib vs. 27.4% after chemotherapy, stable disease (20.4% vs.48.4%) and progressive disease in only 8.2% vs. 21%. This is in accordance with several preclinical and clinical trials demonstrating the efficacy of radiotherapy and concurrent erlotinib in patients with unresectable NSCLC.[15,16]

Cytotoxic drugs alone have limited success in improving on the typical median overall survival (OS) period of 8-11 months.[17] However, erlotinib in second-line setting has shown to delay progression and prolong survival.[18,19] The Study of Coronary Atheroma by Travascular Ultrasound: Effect of Rosuvastatin Versus AtorvastatiN (SATURN) trial demonstrated a significant improvement in median PFS with maintenance erlotinib (12.3 weeks compared to 11.1 weeks in placebo group).[6] Similarly in another clinical trial, a study with predominantly Asian population, PFS was notably prolonged with chemotherapy plus erlotinib versus chemotherapy plus placebo (median PFS 7·6 months vs. 6·0 months). Median OS for patients in the erlotinib and placebo groups were 18·3 months and 15·2 months, respectively.[20] Our survival curves showed PFS of 7.4 months and OS of 12.9 months for stage III NSCLC. Similarly, for stage IV, PFS of 2.8 months and OS of 5.5. months were noted. Irrespective of stage, 1-year survival rate was 41% and 2-year survival was 14%.

Several studies have shown erlotinib therapy to be generally well tolerated.[21] The addition of erlotinib to radiotherapy did not appear to aggravate toxicities and adverse events have been manageable.[9] Adverse events related to radiotherapy include radiation dermatitis, oesophagitis and pneumonitis, while erlotinib-related side effects are mainly skin rash and diarrhoea.[13] Less common toxicities include raised amino-transferase levels[22,23] and depression of cell lines.[24] In this study, too, the most common side effects observed were rash (61.2%), fatigue (42.9%) and diarrhoea (36.7%). On the whole the treatment was generally well tolerated with the exception of five patients with grade III / IV toxicities, necessitating temporary interruption of erlotinib therapy till the severity of symptoms decreased. However, compared with standard chemotherapy, erlotinib is associated with more favourable tolerability.[19,20]

Many studies have shown improved OS, but not the PFS,[25] which the current study did. However, the study was limited by its small sample size and failure to establish subtypes of EGFR mutation. In recent years, a clear benefit of erlotinib has been revealed in EGFR wild type adenocarcinoma too.[26,27] Response of erlotinib must be studied with the help of non-randomised trial to support the current findings and evaluate response in various subtypes of mutation.

Conclusion

Patients with EGFR mutation-positive advanced stage adenocarcinoma of lung, who have previously been treated with platinum-based chemotherapy responded favourably when treated concurrently with erlotinib and radiotherapy followed by maintenance eErlotinib till progression. Promising prospects were seen without significant increase in toxicity.

Disclaimer: The study is based on the MD thesis of one of the authors. The study could not be registered with any official registry so does not have a Trial Number.
Conflict Of Ineterest: None.
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