Original Article

Efficacy and Safety of Afatinib as Second-line Treatment in Advanced Squamous Cell Carcinoma of the Lung : A Retrospective Observational Study

Sk Haidar Ali[1], Suvra Mondal[2], Santu Mondal[3], Amitabha Chakrabarti[4]

Background : Lung Squamous Cell Carcinoma (SqCC) is a challenging subtype of Non-small Cell Lung Cancer with limited treatment options and poor prognosis. Afatinib, an irreversible ErbB family blocker, has shown efficacy as a second-line option after platinum-based Chemotherapy but its role in Indian patients is unclear.

Aims and Objectives : To evaluate the effectiveness, safety and Quality of Life (QoL) of afatinib in Indian patients with advanced lung SqCC after platinum-based chemotherapy.

Materials and Methods : This retrospective study included 110 patients with stage III or IV lung SqCC who received first-line chemotherapy followed by afatinib. Tumor assessments were performed every 8 weeks until progression, Adverse Events (AEs) were graded using CTCAE and QoL was assessed using GHS/QoL scale.

Results : The median age was 65 years, 83.6% were males, 84% were non-smokers and 80% were at stage IV. Afatinib resulted in a median Progression Free Survival (PFS) of 3.7months, an Overall Response Rate (ORR) of 9.7%, and a Disease Control Rate (DCR) of 45%. The most common grade 2 AEs were Diarrhea (38%), Rash/acne (32%) and Stomatitis (11%) and the most common grade 3 AEs were Diarrhea (7%) and Stomatitis (3%). QoL improved in 31.7% of patients, pain reduced in 36.7%, cough alleviated in 41.7% and dyspnea improved in 55%. These findings are consistent with the LUX-Lung 8 trial.

Conclusions : Afatinib is an effective and safe second-line treatment for advanced lung SqCC after platinum-based chemotherapy in Indian patients. Afatinib also improves QoL and symptom control in this population. Future research should explore biomarkers and resistance mechanisms to afatinib in lung SqCC.

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Key words **: Afatinib, Lung Squamous Cell Carcinoma (SqCC), Second-line Treatment.**

Lung cancer is the most common and deadly type of Cancer Worldwide[1]. Lung Squamous Cell Carcinoma (SqCC) is a subtype of Non-small Cell Lung Cancer (NSCLC) that affects 20-30% of NSCLC patients[2]. Unlike lung adenocarcinoma, another subtype of NSCLC, lung SqCC has limited treatment options and poor prognosis[3]. Lung SqCC is characterized by high genetic diversity and complexity, with mutations in many genes and pathways[2,4]. Some of these mutations affect the Epidermal Growth Factor Receptor (EGFR), which is a target for some drugs[4,5]. However, the EGFR mutations in lung SqCC are different from those in lung adenocarcinoma and the response to EGFR inhibitors is usually low and short-lived[5,6].

The standard first-line treatment for advanced/metastatic lung SqCC is Chemotherapy or Immunotherapy, either alone or in combination[7,8]. Immunotherapy is a type of treatment that boosts the Immune system to fight cancer cells[8]. Pembrolizumab is an example of an immunotherapy drug that works by blocking a protein called PD-1 on immune cells[9]. However, not all patients benefit from Immunotherapy, and some may develop resistance over time[10]. For patients who progress after first-line treatment, there are few effective options available. The choice of second-line or later treatment depends on the previous treatment and the patient's condition. Generally, drugs with different mechanisms of action are preferred to avoid cross-resistance[11,12].

Afatinib is a drug that blocks the signaling of all ErbB family members, including EGFR[13]. Afatinib has shown efficacy in patients with EGFR mutation-positive NSCLC and is approved as first-line treatment in this indication[14]. However, afatinib is not recommended as

Editor's Comment :

- Afatinib offers an effective treatment alternative for advanced Squamous Cell Carcinoma lung in place of costly Immunotherapy in our real world scenario. It also has the benefit of oral domiciliary treatment with manageable toxicity profile.

Department of Radiotherapy, R G Kar Medical College & Hospital, Kolkata 700004

[1]MBBS, MD (Radiotherapy), Medical Teacher Trainee Reserve

[2]MBBS, MD (Radiotherapy), Senior Resident

[3]MBBS, MD (Radiotherapy), Assistant Professor, Department of Radiotherapy, IPGME&R Medical College & Hospital, Kolkata 700020

[4]MBBS, MD (Radiotherapy), Associate Professor and Corresponding Author

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first-line therapy for unselected patients with Squamous Cell Lung Cancer and wild-type EGFR[7,15]. Afatinib has demonstrated efficacy as second-line therapy in patients with metastatic Squamous Cell Lung Cancer following progression on Platinum-based chemotherapy, and is approved by the US FDA for use as monotherapy in this patient population[13]. However, the inclusion of afatinib as a second-line treatment option for patients with Squamous Cell Lung Cancer varies across treatment guidelines, reflective of the changing treatment landscape in recent years. The approval of afatinib for use in patients who have progressed on Platinum-based Chemotherapy was based on results from the open-label, Phase III LUX-Lung 8 study, which compared the second-line use of afatinib with erlotinib in patients with advanced Squamous Cell Lung Cancer[15]. Currently, there is a paucity of data on outcomes of afatinib treatment in Indian patients with advanced SCC of the lung.

Aims and Objectives

- To assess the efficacy of afatinib treatment in Indian patients with advanced SqCC of the lung who were treated prior platinum-based Chemotherapy.
- To evaluate the patient-reported outcomes of afatinib treatment in these patients, including Quality of Life (QoL).

Materials and Methods

This is a Retrospective study of 110 patients conducted from January, 2019 to December, 2022 with advanced/metastatic SqCC of the lung who received first-line Platinum-based-Chemotherapy, followed by Afatinib. Afatinib (40 mg) was given orally once daily and adjusted according to tolerability. Treatment was continued until disease progression, unacceptable AEs or withdrawal. Eligible patients were aged 18 years or older with stage IIIor IV NSCLC of squamous histology who progressed after at least four cycles of platinum-based Chemotherapy. Other inclusion criteria were: ECOG performance status within 2, measurable disease, and adequate organ function.

Exclusion criteria : Previous treatment with EGFR-targeted agents; active brain metastases; radiotherapy within 4 weeks; other malignancies within the past 3 years; pre-existing interstitial lung disease; significant gastrointestinal or cardiovascular disorders; any serious illness or organ dysfunction; active hepatitis B, C, or HIV infection; contraindications for afatinib; hypersensitivity to afatinib or its excipients; major surgery within 4 weeks; previous participation in an afatinib trial; use of any investigational drug within 4 weeks; and patients without progressive disease.

Tumour assessments were done by CT or MRI scan at baseline and every 8 weeks until progression or withdrawal. Adverse events were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) (version 5.0). Safety laboratory assessments were done at baseline, on the first visit of each cycle, and at the end of treatment. Patient-reported outcomes were assessed at the first visit of each cycle using Global Health Status/Quality of Life (GHS/QoL) scale.

The aims were to assess Progression Free Survival (PFS), Objective Response Rate (ORR) and Disease Control Rate (DCR), defined as Complete Response (CR), Partial Response (PR), Stable Disease (SD), or Progressive Disease (PD) and incidence of moderate to severe Adverse Events (AEs).

Results

Demographic characteristics and pertinent medical history data were extracted from the medical records of the 110 patients diagnosed with advanced/metastatic Squamous Cell Carcinoma (SqCC) of the lung who were included in the study.

Among the total cohort of 110 patients, a majority of 83.6% (N=92) were identified as male and their median age was 65 years (range: 36-84 years).

The baseline Eastern Cooperative Oncology Group Performance Status (ECOG PS) distribution revealed that 65.5% (N=72) of the patients were categorized under ECOG PS 1, followed by 31.8% (N=35) of patients who were classified as ECOG PS 0 (Table 1).

Within the cohort of patients under consideration, a substantial majority of 84% (N=92) comprised Non-smokers, encompassing both formerly smokers 12% (N=13) and never Smokers 72% (N=79), while 16% (N=18) were identified as current Smokers (Fig 1).

At the commencement of the study, a significant 80% (N=88) of the participants were diagnosed at stage IV, whereas the remaining patients were distributed across stage III with 4.5 % (N=5) at stage IIIA and 15.5 % (N=17) at stage IIIB and IIIC (Table 2).

Among the participants at study inclusion, 60% (N=66) received Carboplatin-based Chemotherapy, while 40% (N=44) were administered Cisplatin-based Chemotherapy as the primary treatment (Fig 2).

The median follow-up duration was 12 months. The administration of afatinib resulted in a median Progression-free Survival (PFS) of 3.7 months. Notably, significant disease control was achieved in 45% (N=50)

Table 1 — *Performance status wise distribution of patients*

Performance Status (ECOGPS)	No of patients (%)
0	35(31.8)
1	72(65.5)
2	3(2.7)

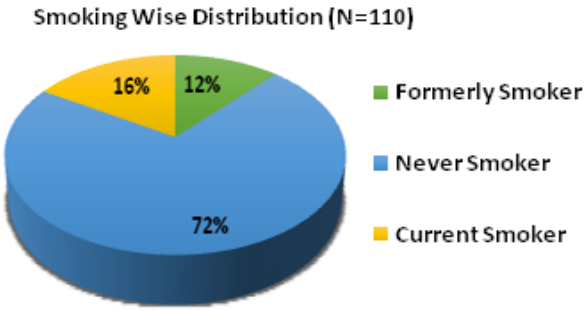

Fig 1 — Smoking status wise distribution of patients

of patients, with a few cases being deemed not evaluable (N=18). Over a median follow-up of 12 months, 2.7% (N=3) of patients exhibited complete response and 7% (N=8) demonstrated partial response, culminating in an overall disease control rate of 45% (Table 3).

Among the treatment-related adverse events observed, the most prevalent grade 2 events associated with afatinib included Diarrhea (38%), Rash/acne (32%), and stomatitis (11%). Notably, the incidence of significant grade 3 adverse events related to treatment was limited to diarrhea (7%) and Stomatitis (3%), with no notable incidence of grade 4 adverse events observed among patients treated with afatinib (Table 4).

The study's assessment of patient-reported outcomes revealed noteworthy improvements in various domains. Specifically, a considerable percentage of patients reported enhanced scores for Global Health Status/Quality of Life (31.7%), Pain reduction (36.7%), and alleviation of Cough (41.7%). Particularly significant was the proportion of patients experiencing improved Dyspnea, which amounted to 55% (Fig 3).

Discussion

The results of this study suggest that afatinib is a viable second-line treatment option for patients with advanced/metastatic Squamous Cell Carcinoma (SqCC) of the lung who have progressed after Platinum-based Chemotherapy. Afatinib showed a favorable efficacy and safety profile, as well as improved patient-reported outcomes, in this real-world setting. These findings are consistent with those of the LUX-Lung 8 trial, which was a randomized, open-label, phase III study that compared afatinib with erlotinib in patients with advanced SqCC of the lung who had progressed after at least one line of Platinum-based Chemotherapy. In that trial, afatinib significantly prolonged Progression-Free Survival (PFS) and Overall Survival (OS) compared with erlotinib with median PFS of 2.6 *versus* 1.9 months [Hazard Ratio (HR) 0.81, 95% Confidence Interval (CI) 0.69-0.95; p = 0.0077] and median OS of 7.9 *versus* 6.8 months (HR 0.81, 95% CI 0.69-0.95; p = 0.0077), respectively. Afatinib also demonstrated a higher Objective Response Rate (ORR) of 6% versus 3% (p = 0.0296) and a longer duration of response of 18.4 versus 13.1 weeks. The most common Adverse Events (AEs) associated with afatinib were Diarrhea, Rash/acne and Stomatitis, which were generally manageable with supportive care and dose adjustments.

Table 2 — *Stage wise distribution of patients*

Stage	No of patients	Percentage
IIIA	5	4.5%
IIIB	7	6.4%
IIIC	10	9.1%
IV	88	80%

Table 3 —*Tumour Response: progression free survival, objective response rate and disease control rate*

Treatment Outcome	Afatinib treated patients
Median PFS (months)	3.7
Complete Response (CR)	3 (2.7%)
Partial Response (PR)	8 (7%)
Stable Disease (SD)	39(35.3%)
Disease Progression (DP)	42(38.18%)

Table 4 — *Treatment-related adverse events*

Adverse Event (CTCAE v5.0)	Grade 2	Grade 3	Grade 4
Diarrhoea	38%	7%	<1%
Rash or acne	32%	3%	
Stomatitis	11%	2%	
Fatigue	4%	<1%	
Nausea	3%	<1%	
Decreased appetite	1%	<1%	

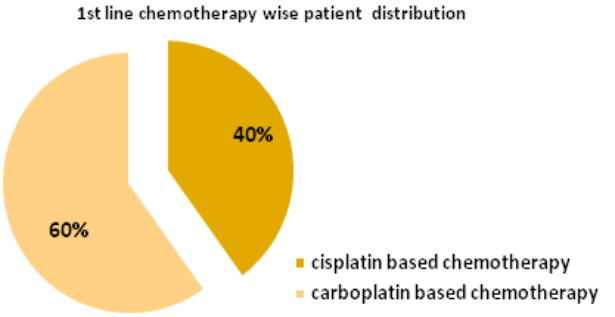

Fig 2 — 1st line treatment wise distribution of patients

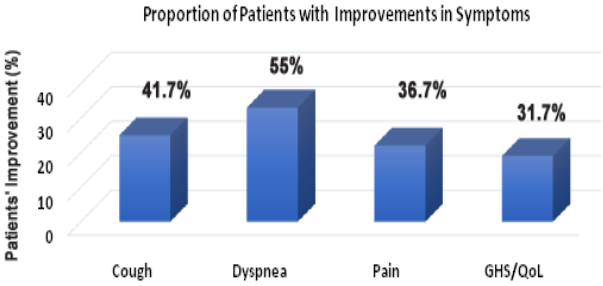

Fig 3 — Proportion of Patients showing Improvements in Symptoms

The LUX-Lung 8 trial was the first to demonstrate a survival benefit for a second-generation EGFR inhibitor over a first-generation EGFR inhibitor in patients with advanced SqCC of the lung. However, the LUX-Lung 8 trial had some limitations, such as the exclusion of patients who had received prior immunotherapy or targeted therapy the lack of biomarker analysis, and the potential selection bias due to the open-label design. Therefore, real-world data are needed to complement the results of the LUX-Lung 8 trial and to provide more evidence on the effectiveness and safety of afatinib in different patient populations and clinical settings.

The present study is one of the few real-world studies that have evaluated afatinib as a second-line treatment for advanced/metastatic SqCC of the lung. The results of this study are in line with those of the LUX-Lung 8 trial, showing that afatinib has a favorable efficacy and safety profile in this setting. The median PFS of 3.7 months observed in this study is higher than that reported in the LUX-Lung 8 trial (2.6 months), which may be attributed to the differences in patient characteristics, such as age, smoking status, ECOG PS, and prior treatment history. The ORR of 9.7% and the disease control rate of 45% observed in this study are also comparable to those reported in the LUX-Lung 8 trial (6% and 50%, respectively). The AEs associated with afatinib in this study were mostly mild to moderate and manageable with supportive care and dose adjustments, similar to those reported in the LUX-Lung 8 trial. The most common grade 2 AEs were Diarrhea (38%), Rash/acne (32%) and Stomatitis (11%), and the most common grade 3 AEs were Diarrhea (7%) and Stomatitis (3%). No grade 4 AEs or treatment-related deaths were observed in this study.

In addition to the efficacy and safety outcomes, this study also assessed the patient-reported outcomes. The results showed that afatinib improved several domains of quality of life, such as Global health status/quality of life, pain, cough, and dyspnea. These improvements are clinically meaningful and reflect the positive impact of afatinib on symptom control and functional status in patients with advanced SqCC of the lung. These findings are also consistent with those reported in a post-hoc analysis of the LUX-Lung 8 trial, which showed that afatinib significantly delayed the time to deterioration of cough and dyspnea compared with erlotinib.

Conclusions

In conclusion, this study provides real-world evidence on the effectiveness and safety of afatinib as a second-line treatment for patients with advanced/metastatic SqCC of the lung who have progressed after Platinum-based Chemotherapy in Indian patients. The results of this study are in line with those of the LUX-Lung 8 trial and support the use of afatinib in this setting. Afatinib showed a favorable efficacy and safety profile, as well as improved patient-reported outcomes, in this real-world setting. Further studies are needed to explore the potential biomarkers and mechanisms of resistance to afatinib in patients with advanced SqCC of the lung.

Limitations of the study :

- The study did not include a control arm, so it is not possible to say definitively that afatinib was responsible for the observed improvements in survival and quality of life.
- The follow-up period was relatively short, at only 12 months. This makes it difficult to assess the long-term effects.

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