Original Article

Clinical Experience on Use of Oral EGFR-TKIs as First-line Treatment of Advanced NSCLC from a Tertiary Care Centre in North India and Implications of Skin Rash

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Abstract

Background. Limited data are available from India on treatment outcomes with oral epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) in newly diagnosed non-small cell lung cancer (NSCLC). We studied the demographic profile and treatment outcomes of patients with NSCLC, receiving first-line treatment with oral EGFR-TKIs.

Methods. Retrospective study of newly diagnosed NSCLC patients treated with oral EGFR-TKIs over a 4-year period at a tertiary care institute in North India.

Results. Of 76 patients studied, females and non-smokers constituted 32.9% and 48.7%, respectively. Majority of patients had adenocarcinoma (59.2%), stage IV (64.5%) disease and Karnofsky performance status ≤70 (74.5%). Gefitinib was the most frequently used EGFR-TKI (92.1%). Most common indication for the use of EGFR-TKIs was poor performance status (65.8%). Among assessable patients, disease control and progressive disease were evident in 66% and 34%, respectively. Most common side effects were skin rash (17%) and diarrhoea (10.6%). Patients with and without skin rash differed significantly in relation to objective response to treatment (100% *versus* 23.1%) and overall survival (median not reached *versus* 178 days). On multivariate logistic regression analysis, malignant pleural effusion was associated with occurrence of rash (odds ratio=0.19; 95% confidence interval = 0.04-0.95; p=0.04).

Conclusions. Oral EGFR-TKIs appear to be useful for the treatment of clinically selected patients with advanced NSCLC. Occurrence of skin rash was independently associated with treatment response and better survival in the current study.
[Indian J Chest Dis Allied Sci 2014;56:149-152]

Key words: Lung cancer, Epidermal growth factor receptor, Tyrosine kinase inhibitor, Skin rash, Overall survival.

Introduction

Oral epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) are an important component of therapeutic armamentarium for advanced non-small cell lung cancer (NSCLC), especially for patients with poor performance status (PS) or those unwilling for systemic chemotherapy. In the recent past, there has been a paradigm shift regarding use of EGFR-TKIs as first-line treatment for advanced NSCLC with clinical selection (female, non-squamous histology, never/light smokers, East Asians) giving way to molecular selection (presence of sensitising mutations in the EGFR gene).[1-3] There continues to be paucity of data from India and South Asia, in general, in the context of use of EGFR-TKIs in treatment-naïve advanced NSCLC. Herein, we report our experience on the use of EGFR-TKIs as first-line treatment for NSCLC.

Material and Methods

A retrospective analysis of newly diagnosed NSCLC patients who received first-line treatment with EGFR-TKIs over a 4-year period (January 2008 to December 2011) at our centre, an apex referral government health care institute in North India, was carried out. Data regarding demographic characteristics (including age, gender and smoking status), histological type, stage of disease and PS were recorded in all patients at the time of treatment initiation as described in detail previously.[4-6] Radiological response to treatment was assessed using Response Evaluation Criteria in Solid Tumours (RECIST).[7] Toxicity was graded as per Common Toxicity Criteria (CTC v3.0).[8] Numerical and categorical data were compared between groups using Mann-Whitney U-test and Chi-square test, respectively. Cox proportional-hazards regression model was used for the analysis of overall survival (OS) and calculation of hazard ratio (HR) with 95% confidence intervals (CIs). Furthermore, in order to test the association between occurrence of skin rash and OS, we also performed Cox proportional-hazards analyses for best-case-scenario and worst-case-scenario. Kaplan-Meier method was used for calculating median OS and log-rank test used for assessing group

[Received: April 1, 2013; accepted after revision: April 17, 2014]

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differences. Logistic regression analysis was carried out for factors associated with occurrence of skin rash.

Results

Of the 76 patients studied, males and current/ex-smokers constituted 67.1% (n=51) and 51.3% (n=39), respectively. Histological distribution was as follows: adenocarcinoma (n=45; 59.2%), squamous cell carcinoma (n=18; 23.7%), NSCLC-NOS (not otherwise specified) (n=9; 11.8%) and large cell carcinoma (n=4; 5.3%). Majority of the patients were in stages IV (n=49; 64.5%) and IIIB (n=20; 26.3%). Malignant pleural effusion was present in 20 (26.3%) patients. Baseline Karnofsky PS was 80-100 in 25.5%, 60-70 in 42.6% and less than or equal to 50 in 31.9%. Gefitinib (n=70, 92.1%) was the most frequently used EGFR-TKI. Most common indications for EGFR-TKI use were poor PS in 65.8% (n=50) and unwillingness for chemotherapy in 27.6% (n=21). Overall, 17 (22.4%) patients were lost to follow-up and 47 (61.8%) patients had atleast one follow-up visit after one month and were eligible for assessment of response and toxicity. None of the assessable patients had a complete response; partial response (PR), stable disease and progressive disease were documented in 36.2%, 29.8% and 34.0%, respectively. The most common side effects were skin rash and diarrhoea, developed in 17.0% and 10.6% patients, respectively. Severity of rash was grade 1 in 8.5%, grade 2 in 6.4% and grade 3 in 2.1% patients, respectively while severity of diarrhoea was grade 1 in 8.5% and grade 2 in 2.1% patients, respectively. Objective PR was observed in all (100%) patients with skin rash as compared to 23.1% among those without skin rash ($p<0.001$). On Kaplan-Meier analysis for worst-case-scenario, median OS in patients without skin rash was 178 days [95% CI=111-245 days] while among those with skin rash, median OS had not been reached (log rank p=0.046). In case of best-case-scenario analysis, the median OS in patients without skin rash was 60 days (95% CI=14-106 days) while among those with skin rash, median OS had not been reached (log rank p=0.012). The positive prognostic effect of skin rash on survival was found for both best-case-scenario (HR=0.25; 95% CI=0.08-0.81; p=0.021) and worst-case-scenario analyses (HR=0.32; 95% CI=0.10-1.04; p=0.059). Survival of patients with and without skin rash is given in the figure.

Skin rash occurred in 25.0% and 5.4% of patients with and without malignant pleural effusion (p=0.026), respectively. Gender, histology and smoking status did not differ amongst patients with and without skin rash. On multivariate logistic regression analysis, only malignant pleural effusion was associated with the occurrence of rash (odds ratio=0.19; 95% CI=0.04-0.95; p=0.04).

Discussion

The present report, to the best of our knowledge is the first from North India documenting the utility of EGFR-TKIs as first-line treatment of advanced NSCLC. Louis *et al* [9] from South India recently reported results of their retrospective analysis on the efficacy of oral EGFR-TKIs as compared to standard chemotherapy in treatment naïve patients with advanced NSCLC.[9] A comparison of demographic characteristics and outcomes in all newly diagnosed NSCLC patients at the authors' institute, NSCLC patients treated with oral EGFR-TKIs in the present study and in the previously published study from South India[9] is presented in the table. Although the disease control rates (complete response + partial response + stable disease) were similar in both the studies, our patients had shorter median OS 184 days (95% CI=114-254) compared to the 10 months (300 days) observed in the south Indian study.[9] The likely explanations for this include greater percentage of females, non-smokers and non-squamous histology in the study by Louis *et al* [9], all of which are positive prognostic factors as well as positive predictive factors for clinical benefit with EGFR-TKIs.[10] The only other notable publication from India on EGFR-TKIs was a subgroup analysis of the Iressa Survival Evaluation in

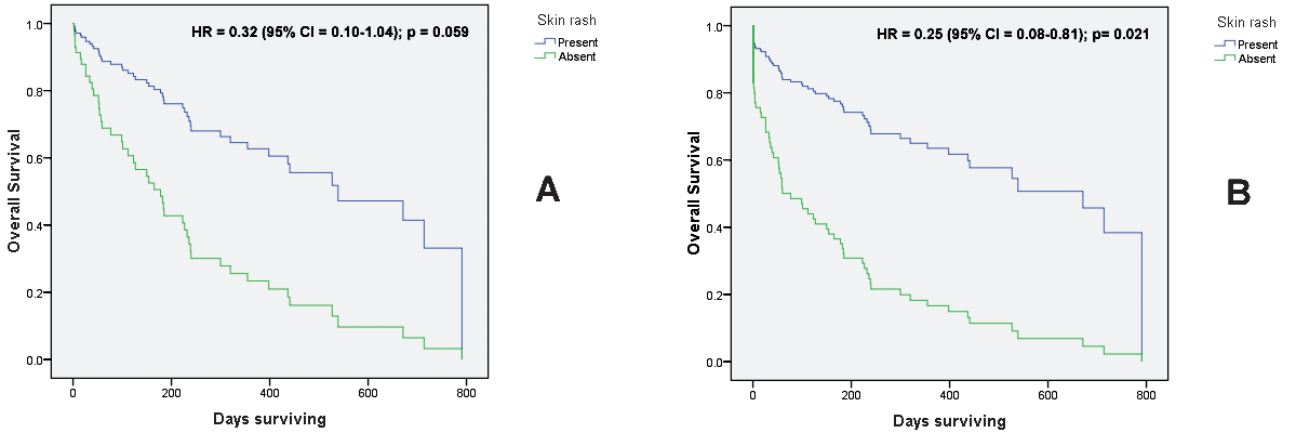

Figure. Probability of overall survival for patients who developed skin rash (any grade) with oral EGFR-TKI treatment as compared to those who did not. Panels A and B represent worst-case and best-case scenario, respectively. HR=Hazard ratio; CI=Confidence interval.

Table. Comparison of demographic characteristics and outcomes in all newly diagnosed patients of NSCLC at the authors' institute, NSCLC patients treated with oral EGFR-TKIs in the present study and in the previously published study from South India

	All Newly Diagnosed NSCLC	Patients Treated with Oral EGFR-TKIs	
		Present study	Louis *et al* [9]
No. of cases	520	76	47
Age (years) [mean (SD)]	58.7 (10.8)	64.6 (12.6)	N.A.
Females (%)	17.9	32.9	42.6
Non-smokers (%)	26.0	48.7	70.2
Performance status			
Karnofsky100-90 (%)	62.5	21.3	N.D.
Karnofsky 80 (%)	15.6	04.3	N.D.
Karnofsky ≤70 (%)	21.9	74.4	N.D.
ECOG 1	N.D.	N.D.	23.4
ECOG 2	N.D.	N.D.	66.0
ECOG 3	N.D.	N.D.	10.6
ADC and large cell (%)	38.4	64.5	100
NSCLC-Undiff (%)	13.7	11.8	0
Stage			
I-IIIA (%)	16.1	09.2	0
IIIB (%)	35.4	26.3	6.4
IV (%)	48.5	64.5	93.6
Objective responses			
Partial response	N.D.	36.2%	23.4%
Stable disease	N.D.	29.8%	42.6%
Progressive disease	N.D.	34.0%	34.0%
Overall survival (days) [median (range)]	N.D.	184 (114-254)	300 (N.D.)
1-year overall survival (%)	N.D.	18.8	44.3

Definitions of abbreviations: NSCLC=Non-small cell lung cancer; EGFR-TKIs=Epidermal growth factor receptor-tyrosine kinase inhibitors; SD=Standard deviation; N.A.=Not applicable; ECOG=Eastern Cooperative Oncology Group; N.D.=Not described; ADC=Adenocarcinoma; NSCLC-Undiff =Undifferentiated non-small cell lung cancer.

Lung Cancer (ISEL) randomised trial (which had compared gefitinib to placebo as second-/third-line treatment of advanced NSCLC patients who had refractory/relapsed disease).[11] Data from the Indian arm of the ISEL trial was published separately.[12] However, since treatment naïve and pre-treated patients differ significantly in their tolerability and responses to treatment, we did not compare the findings of our study and the study by Louis *et al* [9]; both of which reported the utility of usage of EGFR-TKIs rather than their usage as part of a randomised controlled trial.[12] In addition, Table given above also highlights differences in the key baseline and demographic characteristics at our centre between population of all NSCLC patients (most of whom received chemotherapy as the first-line treatment) and the cohort of NSCLC patients treated with EGFR-TKIs alone (as the first line treatment) with the latter having a greater percentage of females, non-smokers, non-squamous histology, suboptimal PS and stage IV disease.[13]

It is worthwhile mentioning here that routine molecular selection of patients is hampered by economic and infrastructural constraints related to availability of testing for EGFR mutations.[14] Recently, in the phase III randomised (TOPICAL) trial assessing efficacy of erlotinib as compared to placebo in the first-line treatment for patients with advanced NSCLC who are unfit for chemotherapy, occurrence of skin rash was the only clinical characteristic that was shown to correlate with improvement in OS from use of erlotinib.[15] In a meta-analysis involving patients (pre-treated as well as treatment naïve) who received EGFR-TKIs, occurrence of skin rash was found to be an independent predictor for improved OS, progression free survival (PFS) and objective response rates (ORRs).[16]

Two important facts are highlighted from the results of the current study. First, clinically selected patients with advanced NSCLC who either have a poor PS or are unwilling for chemotherapy can benefit from the use of commercially available EGFR-TKIs (gefitinib and erlotinib) even in the absence of biomarker availability as evidenced by the fact that disease control was achieved in almost two-thirds of patients in our study. When compared with the TOPCIAL trial,[15] inherent differences, namely diversity in ethnicity (Caucasians *versus*

Indians) and geographical location of the study populations, study design (retrospective real-life scenario *versus* prospective randomised clinical trial) and patient numbers could account for some of the differences observed in relation to disease control rates.[15] Second, our analysis indicates that occurrence of skin rash is a reasonably strong surrogate for clinical benefit with EGFR-TKIs both in terms of objective response and OS — the latter also being supported by the results of the TOPICAL trial.[15] The positive predictive association of skin rash with better OS amongst patients being treated with EGFR-TKIs in our study was seen for both best-case-scenario and worst-case scenario analyses. In the meta-analysis on skin rash in EGFR-TKIs treated patients, no subgroup analysis was performed for the five studies involving treatment-naïve patients.[16] Moreover, these five studies had patient numbers that were either less than or comparable to ours, were from regions other than South-Asia and involved predominantly or exclusively adenocarcinoma histology. It is worthwhile to note that even patients with squamous cell carcinoma histology may benefit from EGFR-TKI treatment and for this purpose a combination of high EGFR gene copy number as determined by florescent *in-situ* hybridisation (FISH) and skin rash is a better predictor of benefit than the former alone.[17]

Based upon the findings of the present study, it may also be suggested that the presence of malignant pleural effusion at the time of treatment initiation can serve as a crude predictor for the occurrence of skin rash and in turn for objective response as well as better OS – an analysis that has not been performed in either the TOPICAL trial[15] or the meta-analysis[16] discussed earlier. Testing for the presence of sensitising EGFR mutations shall continue to remain the preferred modality for choosing patients for whom this class of drugs should be initiated upfront and this communication is neither intended to nor does it have the statistical power to undermine its importance.[10,18] We hope future studies can aim to assess and hopefully answer the key question and hypothesis that has been generated in our study, namely, the association between presence of malignant pleural effusion at diagnosis with presence of EGFR mutations and with the occurrence of skin rash during EGFR-TKIs therapy. This could have important implications for resource-limited settings wherein routine testing for EGFR mutations may not be always possible.

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