Third-line therapy in the epidermal growth factor receptor mutation-positive advanced nonsmall-cell lung cancer

Vanita Noronha, Nikhil Pande, Amit Joshi, Vijay Patil, Vaishakhi Trivedi, Anuradha Chougule, Amit Janu[1], Abhishek Mahajan[1], Vikas Talreja, Kumar Prabhash

Abstract

Introduction: The treatment of lung cancer is not defined in the third-line setting and remains an unanswered question. Erlotinib is the only drug approved in the third-line setting. With the introduction of effective first- and second-line therapies, more and more patients warrant an effective third-line therapy. We did a *post hoc* analysis of our randomized trial for the epidermal growth factor receptor (EGFR)-positive patients who received third-line therapy. **Materials and Methods:** The present series is of 85 patients who received third-line therapy. Demographic data were collected which included age, performance status, gender, stage, comorbidities, and sites of metastasis. Data were collected for the type of systemic treatment patients received and number of cycles received. Information related to the impact of treatment on the symptoms of patients and the imaging done for response evaluation was collected. **Results:** Of the 85 patients, there were 13 patients (15%) who achieved a partial response and 34 patients (40%) who had stable disease as best response. There were no complete response and 20 patients (24%) had disease progression at the time of first assessment. The median overall survival (OS) was 8.36 months (95% confidence interval [CI] 6.8–9.8 months) and median progression-free survival was 4.4 months (95% CI 3.3–4.9 months). Grade 3 or 4 toxicities were seen in 42.5% (n = 36) of the total patients. **Conclusions:** The study provides the patterns and outcomes of systemic treatment in metastatic EGFR-mutated lung adenocarcinoma in patients who have progressed on two or more lines of systemic therapies. This data suggest that third-line systemic therapy may provide meaningful outcomes in these patients.

Key words: Epidermal growth factor receptor-positive, nonsmall-cell lung cancer, third-line therapy

Introduction

The treatment for advanced nonsmall-cell lung cancer (NSCLC) is fairly well-defined in the first-line and second-line settings.[1,2] There are very few studies regarding third-line therapy as compared to that of the first and second line. This may be because at the best very few patients make it to third-line treatment and even fewer with good performance status (PS) tolerate third-line therapy. A large randomized trial evaluated the use of erlotinib as third-line treatment for advanced NSCLC and resulted in its approval for same, making it the only agent approved for the same.[2] With the introduction of effective first- and second-line therapies, more and more patients are now alive and in good PS to warrant consideration of third-line therapy. In the epidermal growth factor receptor (EGFR)-negative patients, erlotinib remains an accepted option in the third-line setting, but in the EGFR-positive patients, data are more limited. Relevant data in this setting are important to guide clinicians in clinical practice.

We did a *post hoc* analysis of our randomized trial for EGFR-positive patients who received third-line therapy. We analyzed their outcomes, different regimens used, and toxicities.

Materials and Methods

The current study is a *post hoc* analysis of the patients evaluating the use of tyrosine kinase inhibitor (TKI) (gefitinib) versus platinum doublet in the first line conducted in the outpatient department of the thoracic medical oncology unit at a tertiary care oncology center in Mumbai, India.[3]

The patient inclusion criteria included the following:

1. Pathologically-proven NSCLC patients who were Stage IIIB or IV at the time of diagnosis and were EGFR mutation-positive using reverse transcription-polymerase chain reaction
2. Patients who had received chemotherapy or targeted therapy and had progressed on them in the second line and still maintained a good PS (Eastern Co-operative Oncology Group 0–2)
3. They should have received at least one cycle of third-line therapy.

Pretreatment evaluation

Demographic data were collected which included age, PS, gender, stage, comorbidities, sites of metastasis, and smoking history. Findings in imaging studies were noted at baseline before the start of third-line therapy for response evaluation in future.

Treatment and follow-up

Data were collected for the type of systemic treatment patients received and number of cycles received. Data for side effects were collected and grading for severity done as per the common terminology criteria for adverse events (CTCAE) version 4.02. Information related to the impact of treatment on the symptoms of patients and the imaging done for response evaluation was collected. Response evaluation was done as per the response evaluation criteria in solid tumors (RECIST) version 1.1 criteria. Imaging with computerized tomography was done once every 2–3 months or on clinical suspicion of progression.

Statistical analysis

All the data were entered, and statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) software version 22.0. Descriptive statistics were performed for demographic data. Median follow-up was calculated for the surviving patients from the date of diagnosis

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Departments of Medical Oncology and [1]Radiology, TMH, Mumbai, Maharashtra, India
Correspondence to: Dr. Kumar Prabhash, E-mail: kprabhash1@gmail.com

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to the date of last follow-up. Patients who had not progressed at the time of last follow-up were censored. Progression was defined as clinical deterioration or radiological progression. Progression-free survival was calculated from the date of starting third-line therapy to the date of progression or date of death if patients died before disease progression or date of change of treatment before progression of the disease. Overall survival (OS) was calculated from the date of starting third-line therapy to death from any cause. The Kaplan–Meier curve was plotted for the progression-free survival (PFS) and the OS in months. The log-rank test was used to compare the PFS and OS in different groups.

Results

There were 290 patients randomized to receive either pemetrexed-platinum or gefitinib as the first-line therapy in the primary study with 145 in each arm. A total of 214 (74%) of them had progressive disease. 169 of these 214 (79%) received second-line therapy.

There were 85 patients with metastatic EGFR-mutated adenocarcinoma progressions who had received third-line therapy were analyzed. Fifty-two (61%) were male and 33 (39%) were female in this cohort [Table 1]. The most common EGFR mutation was Exon 19 mutation 61 (72%) and Exon 21 being the second most common 21 (25%). All patients had received gefitinib before starting the third line with majority receiving pemetrexed (59%) as the first line.

The treatment details are mentioned in Table 2. Taxanes as single agents (paclitaxel (n = 43, 51%) docetaxel (n = 15, 17.6%) were given in 68% of the total patients. Gefitinib was continued beyond progression in 10 (12%) of the patients. Single-agent gemcitabine was used in 6 (7%) of the total patients [Table 2]. These constituted the bulk of treatment options in the third line which were based on treating physicians' discretion after a thorough assessment.

There were 13 patients (15%) who achieved a partial response and 34 patients (40%) who had stable disease as best response. There were no complete response and 20 patients (24%) had disease progression at the time of first assessment [Table 3]. Patients receiving weekly paclitaxel had OS of 10.6 months (95% confidence interval [CI] 6.7–14.4) as compared to 9.8 months (95% CI − 7.5–12.0) when other agents were used (P = 0.5), suggesting that there was no survival difference as compared to other lines [Figure 1]. The other treatment options exercised are mentioned in Table 2.

The median OS was 8.36 months (95% CI 6.8–9.8 months) [Figure 2], and median PFS was 4.4 months (95% CI 3.3–4.9 months) [Figure 3]. Grade 3 or 4 toxicities were seen in 42.5% (n = 36) of the total patients [Table 4].

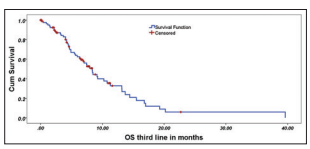

Figure 1: Kaplan–Meier overall survival curves of weekly paclitaxel in months

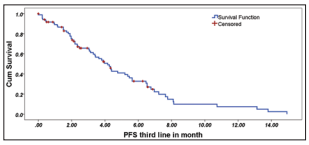

Figure 2: Kaplan–Meier overall survival of third-line drug in months

Discussion

Third-line therapy in NSCLC has been marred with controversies and it remains inconclusive whether third-line therapy should be offered to patients. Erlotinib became the only agent approved in this setting after a large trial found benefit compared to the best supportive care.[2] With the current improvement in regimens and the introduction of targeted therapies and immunotherapy, there remains a significant proportion of patients after the failure of first two lines of therapy who maintain a good PS and would warrant further therapy. There are also studies to show that many patients choose chemotherapy for a small benefit in health outcomes

Table 1: Demographic data and baseline characteristics

Demographic details	Frequency (%)
Sex	
Male	52 (61.2)
Female	33 (38.8)
EGFR mutation	
Exon 21	21 (24.7)
Exon 19	61 (71.8)
Exon 18	3 (3.5)
First-line therapy received	
Pemetrexed with platinum	50 (58.8)
Gefitinib	35 (41.2)

EGFR=Epidermal growth factor receptor

Table 2: Various third-line treatment options given to the metastatic adenocarcinoma lung patients

Treatment	Number of patients (%)
Gefitinib	10 (11.8)
Weekly paclitaxel	43 (50.6)
Gemcitabine	6 (7.1)
Vinorelbine	1 (1.2)
Erlotinib	1 (1.2)
Docetaxel	15 (17.6)
Paclitaxel + carboplatin	2 (2.4)
Oral etoposide	1 (1.2)
Oral cyclophosphamide	2 (2.4)
Etoposide + carboplatin	1 (1.2)
Others	3 (3.5)

Table 3: Various responses of treatment given in the third line in metastatic adenocarcinoma lung patients

Response	Frequency (%)
PR	13 (15.3)
SD	34 (40.0)
PD	20 (23.5)
Not available	18 (21.2)

PR=Partial response, SD=Stable disease, PD=Progressive disease

Table 4: Grade 3/4 toxicities

Toxicities	Number of patients (%)
Anemia	2 (2.4)
Thrombocytopenia	4 (4.7)
Neutropenia	9 (10.6)
Hepatic dysfunction	6 (7.1)
Skin	4 (4.7)
Nausea/vomiting	4 (4.7)
Fatigue	6 (7.1)
Hyponatremia	1 (1.2)
Total	36 (42.5)

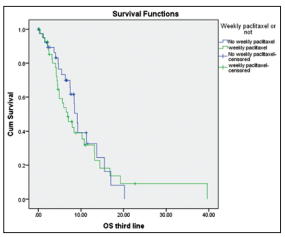

Figure 3: Kaplan–Meir progression-free survival of third-line drugs

even after the adverse effects have been explained and hence would be more accepting to third-line therapy.[4]

The EGFR mutation-positive patients are a unique group who can be started on first-line TKI and usually remain in good PS and tolerate subsequent line of therapy very well.

The introduction of newer generation TKI-like osimertinib is an alternative second line in T790M-positive patients making chemotherapy a possible alternative in third line, but this is so only in 60% of patients. Our *post hoc* analysis of gefitinib against pemetrexed platinum chemotherapy was done when osimertinib was not available in India. This leaves subsequent chemotherapy as the only option in the third line as they have already failed on first-generation oral TKI.

We had a significant 85 (30%) patients of the original 290 who were fit for third-line therapy which although <40% in the Phase III trial of pemetrexed versus docetaxel in the second-line setting was >14% in a large retrospective Austrian analysis for third-line therapy.[5,6]

Weekly paclitaxel at 80 mg/m^2 was the most common regimen used in the present study. This regimen stems from the use of taxanes in the second line and beyond in various trials. Docetaxel weekly has been demonstrated to be both effective and less toxic regimen in multiple trials.[7-9] Gefitinib beyond progression and gemcitabine were the other common regimens used in this study which is keeping with the global trends for the treatment of NSCLC in the third line.[10] The response rates in this study was 15% and disease control rate of 55% which compares similarly with another retrospective analysis examining docetaxel or pemetrexed alone in the third line.[11] The PFS in this study was 4.3 months which appears better than 2.6 months with pemetrexed and 3.8 months with docetaxel in a retrospective study.[11]

The OS was, however, lower in this study at 8.3 months, but weekly paclitaxel in this study had an OS of 10.6 months. In another retrospective analysis, the median OS after the beginning of third or fourth line was only 4 months.[12] Two other single institution retrospective analysis one in Germany[13] with chemotherapy and another in France[14] with TKI as the third line showed an OS of 3.8 and 5.9 months, respectively.

The data for toxicity in third-line therapy are not forthcoming with very little data in the literature. We had neutropenia in approximately 11% of patients and anemia and thrombocytopenia in another 7% of patients as compared to 14% when pemetrexed was used in the third line in a retrospective analysis.[11]

Conclusions

The study provides the patterns and outcomes of systemic treatment in metastatic EGFR-mutated lung adenocarcinoma in patients who have progressed on two or more lines of systemic therapies. This data suggest that third-line systemic therapy may provide meaningful outcomes in these patients. We suggest a prospective clinical trial to develop level 1 clinical evidence.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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