Article published online: 2020-12-28

Efficacy and toxicity profile of maintenance pemetrexed in patients with stage IV adenocarcinoma lung in Indian population

Goyal Pankaj, Batra Ullas, Dinesh Chandra Doval, Jain Parveen, Upadhyay Kumar Amitabh, Prasanta Kumar Dash, Jain Akhil, Agarwal Mohit, Bajaj Rajat

Abstract

Context: Lung cancer has been the most common cancer in the world for several decades. Pemetrexed is recommended as an option for the maintenance treatment in metastatic adenocarcinoma lung, if disease has not progressed immediately following platinum-based chemotherapy. **Aims:** To study efficacy and toxicity profile of pemetrexed as a maintenance chemotherapeutic agent in patients with stage IV adenocarcinoma lung, not progressing after first line chemotherapy. Settings and Design: This was an observational, prospective. We enrolled patients with stage IV adenocarcinoma lung who has not progressed on first line chemotherapy, from September 2013 to August 2014 at a tertiary care cancer institute in North India. **Materials and Methods:** In all, 108 patients with stage IV adenocarcinoma lung were started on induction pemetrexed/platinum chemotherapy. 60 patients with no disease progression & ECOG PS 0-2 were started on Pemetrexed maintenance. Progression free survival (PFS) and toxicity profile were recorded. **Results:** The mean number of maintenance cycles was 8.3 (range 2-28). 13 (21.6%) patients took >10 maintenance cycles. Pemetrexed maintenance therapy resulted in progression free survival (PFS) of 5.4 months. PFS on pemetrexed was consistent for all patient subgroups, including induction response: complete/partial responders (n-31) and stable disease (*n*-29). 14 patients had grade III/IV adverse events with anemia being the most common in 3/60 patients (5%). 3 patients (5%) developed renal dysfunction out of which 1 was grade III. **Conclusions:** Pemetrexed continuation maintenance chemotherapy is active and well tolerated. Pemetrexed maintenance should be considered in patients with advanced adenocarcinoma lung patients who have not progressed on completion of induction chemotherapy.

Key words: Adenocacinoma lung, pemetrexed, pemetrexed maintenance

Introduction

Lung cancer has been the most common cancer in the world for several decades according to Globocon 2012.[1] There were 1.8 million new cases in 2012 (12.9% of the total), 58% of which occurred in the less developed regions. The disease remains the most common cancer in men worldwide (1.2 million, 16.7% of the total) with the highest estimated age-standardized incidence rates in Central and Eastern Europe (53.5/100,000) and Eastern Asia (50.4/100,000). In India, lung cancer is second to oral cancers by incidence in both sexes in India and incidence comparable to oral cancers in males and seventh most common in females. It is among three most common causes of cancer mortality with breast and cervical cancer and the most common cause of cancer death in males.[1]

Approximately, 75% of lung cancers are nonsmall-cell lung cancers (NSCLC) and most of these patients have unresectable metastatic (stage IV) disease with 5-year survival rates that range from 3% to 7%.[2] The main-stay of treatment in stage IV NSCLC is chemotherapy however even with the standard doublet chemotherapy 1 year survival is only 35% with 10–11 months of overall survival (OS) benefit as per the cochrane collaboration group reviewed data from all randomized controlled trials published between January 1980 and June 2006.[3]

Second line trials were done to improve the survival in patients with metastatic lung cancer and docetaxel (75 mg/m^2 every 3 weeks) was the first agent approved by the Food and Drug Administration in view of improvement in 1-year OS over best supportive care (BSC) as second-line therapy[4] followed by approval of pemetrexed on the basis of noninferiority over docetaxel in a second-line trial.[5] Subsequent trials demonstrated the differential activity of tyrosine kinase inhibitors (TKIs) depending on the presence or absence of driver mutations. TAILOR was the first study to demonstrate improved survival with docetaxel over erlotinib in patients with epidermal growth factor receptor (EGFR) wild-type NSCLC.[6]

Despite multiple options available in the second-line setting, clinical outcomes remain poor. Response rates are, on average, <10%, and median survival is 7–9 months from the start of second-line therapy.[7] Hence, new treatment strategies are needed to prolong the survival one of which is maintenance therapy. Maintenance therapy is designed to prolong a clinically favorable state after completion of a predefined number of induction chemotherapy cycles and has two principal paradigms.[8] Continuation maintenance is defined as a continuation of the nonplatinum agent that formed part of the initial therapy and switch maintenance is defined as an immediate switch to an alternative single agent that did not comprise part of the platinum-based first-line chemotherapy.[9]

Second-line chemotherapy is generally administered with disease progression, and although second-line chemotherapy can prolong survival for patients with NSCLC, proportion of patients receiving second-line chemotherapy is only 50–60%,[3,10] most often due to declining performance status (PS).[11-14] The idea of maintenance therapy benefitting lung cancer patients had emerged from the study by Fidias *et al*. who conducted the first phase III trial employing switch maintenance using a modern platinum-based doublet chemotherapy, randomizing 309 patients with IIIB/IV NSCLC

Access this article online
Quick Response Code:
Website: www.sajc.org
DOI: 10.4103/2278-330X.195345

Department of Medical Oncology, Rajiv Gandhi Cancer Institute, Rohini, New Delhi, India
Correspondence to: Dr. Goyal Pankaj,
E-mail: pankaj155@yahoo.com

How to cite this article: Pankaj G, Ullas B, Doval DC, Parveen J, Amitabh UK, Dash PK, *et al*. Efficacy and toxicity profile of maintenance pemetrexed in patients with stage IV adenocarcinoma lung in Indian population. South Asian J Cancer 2016;5:196-203.

after 4 cycles of gemcitabine and carboplatin to immediate docetaxel versus the second line (delayed) docetaxel at a demonstration of progression.[10] Median progression-free survival (PFS) was statistically better with immediate docetaxel, i.e. 5.7 months versus 2.7 months for delayed docetaxel (P = 0.0001) and toxicity profiles were also identical. Only 63% of patients received second-line docetaxel in the delayed docetaxel arm, mostly due to decline in PS and clinical deterioration suggesting that the benefit of switch maintenance docetaxel was likely due to a higher number of patients received second-line chemotherapy. Hence increasing the number of patients on post first line therapy may be necessary to prolong survival in advanced NSCLC.

Since then, maintenance therapy has attracted special attention as a promising novel strategy for treating advanced NSCLC due to its PFS and OS benefits in various trials. Maintenance therapy is traditionally defined as a continuation of chemotherapy without interruption for patients who have achieved an objective response or stable disease (SD) following first-line chemotherapy, with the aim of delaying disease progression.[8,9] It has been seen that administration of platinum-based doublet therapy after four to six cycles increases toxicity without adding any survival benefit.[15,16] Therefore, platinum agents are discontinued after induction chemotherapy and either the nonplatinum agent or a new chemotherapy agent or EGFR tyrosine kinase (if EGFR mutant) inhibitors are continued until progression.

Most of the studies on maintenance therapy are from Western countries and recently paramount trial showed OS and PFS. There is a paucity of such data exclusively from the Indian subcontinent. Hence this study was planned to study the efficacy and tolerability of maintenance chemotherapy in patients with stage IV adenocarcinoma lung not progressing after first line chemotherapy.

Aims and objectives

Primary aim

To study efficacy and toxicity profile of pemetrexed as a maintenance chemotherapeutic agent in patients with stage IV adenocarcinoma lung, not progressing after first line chemotherapy.

Objectives

- To evaluate the PFS of pemetrexed as a maintenance chemotherapeutic agent in patients with stage IV Adenocarcinoma lung
- To compare the time to progression among patients with SD with patients with a partial or complete response (PR/CR) after first-line chemotherapy
- Evaluate the toxicity profile of pemetrexed as maintenance chemotherapy.

Study design

This was an observational, prospective study to evaluate the efficacy and toxicity profile of pemetrexed as a maintenance chemotherapeutic agent in stage IV adenocarcinoma lung in patients not progressing after first line chemotherapy. Patients enrolled from September 2013 to August 2014 at Rajiv Gandhi Cancer Institute (RGCI), a tertiary care cancer institute in India were taken for the study after taking consent.

Patient selection

Inclusion criteria

- Histological or cytological confirmed case of adenocarcinoma lung (stage IV) who has completed first line chemotherapy with 4–6 every 3 weekly cycles of pemetrexed (500 mg/m^2) and platinum (cisplatin 75 mg/m^2 or carboplatin area under the curve 5) combination
- No progression on first line treatment
- Eastern Cooperative Oncology Group (ECOG) PS 0–2.
- Age >18 years, adequate bone marrow reserve (white blood cell [WBC] count: >3500/mm^3, absolute neutrophil count (ANC): >1500/mm^3, platelet count >100 × 10^9/L; and hemoglobin, >9 g/dL), adequate hepatic and renal function (bilirubin <1.5 times the upper limit of normal; alkaline phosphatase and transaminase levels <3.0 times the upper limit of normal or <5 for liver involvement; serum creatinine <1.5 mg/dl, calculated creatinine clearance, >45 mL/min), and adequate birth control measures if in reproductive age group.

Exclusion criteria

- Pregnancy and lactation, uncontrolled sepsis, diabetes or hypertension
- Double malignancy.

Sample size calculation

Patients of lung cancer put on maintenance pemetrexed enrolled from September 2013 to August 2014 at RGCI were taken. Of 94 patients who completed pemetrexed and platinum combination chemotherapy, 60 patients were evaluated for maintenance chemotherapy with pemetrexed.

Patient evaluation

Pretreatment evaluation was done with medical history and physical examination, a complete blood cell (CBC) count, a standard bio-chemical profile (kidney function test [KFT], liver function test [LFT], serum electrolytes), urinalysis for protein, blood, and microscopic examination, calculated creatinine clearance using the modified Cockcroft and Gault formula, chest X-ray, and a radiologic imaging study for tumor measurement, mostly chest computed tomography/positron emission tomography (CT/PET) scan.

Diagnosis of adenocarcinoma lung was based on clinical examination, and histological or cytological confirmation and staging will be done as per American Joint Committee on Cancer Lung Cancer Staging 7th edition.

Information was noted in a performa and patients were reviewed on outpatient department and inpatient department bases. Smokers were defined as per US Centers for Disease Control and prevention guidelines as never smokers (who have never smoked a cigarette or who smoked fewer than 100 cigarettes in their entire lifetime), former smokers (smoked at least 100 cigarettes in their lifetime, but say they currently do not smoke), nonsmokers (who currently do not smoke cigarettes, including both former smokers and never smokers) and current smokers (smoked 100 cigarettes in their lifetime and currently smoke cigarettes every day or some days).[17]

Patients were re-evaluated radiologically with CT chest or PET-CT (RECIST 1.1 criteria) after every 3 cycles of

maintenance chemotherapy initially and every 6 cycles thereafter or symptom-driven interim evaluation if needed.[18] Evaluations before each cycle of therapy included history, physical examination, CBC count, calculation of creatinine clearance, and measurement of blood chemistry values. The duration of any clinical or biochemical toxicity was documented as per CTCAE 4.0 criteria.[19] To administer chemotherapy, patients were required to maintain a WBC >3000/mm^3, ANC >1500/mm^3, platelet count >100,000/mm^3, serum creatinine <1.4 mg% and calculated creatinine clearance more than 45 mL/min based on the standard Cockcroft and Gault formula.

Treatment plan

Maintenance chemotherapy was administered on an inpatient basis/daycare setting at Rajiv Gandhi Cancer Hospital. All patients received oral folic acid (500 ug) daily and a Vitamin B12 injection (1000 ug) every 9 weeks, beginning 1–2 weeks before the first dose and continued until 3 weeks after the last dose of study treatment. Dexamethasone 4 mg was given by mouth twice daily the day before, the day of, and the day after pemetrexed administration. All patients were administered pemetrexed (500 mg/m^2) intravenously over 10 min in 100 ml normal saline on day 1 of 21-day cycles.

Maintenance treatment was started within 21–42 days from day 1 of last induction cycle and continued until disease progression, patient-physician decision, or unacceptable toxicity. Cycle delays of up to 42 days were permitted for recovery from adverse events. The National Cancer Institute Common Toxicity Criteria (v. 4.0) were used to grade side effects. Patients had CBC counts evaluation along with KFT and LFTs before the start of each chemotherapy cycle. Dose reduction was allowed for any grade 3 or grade 4 adverse events.

Evaluation of tumor response

The primary objective of this study was to determine the PFS for patients with stage IV NSCLC (adenocarcinoma) who received treatment with pemetrexed continuation maintenance. Patients who had received at least one cycle of pemetrexed and had follow-up measurements performed to assess change in tumor size were assessable for response. RECIST response criteria (version 1.1) were used to define the antitumor effects; responses were assessed after every 3 cycles, just prior to subsequent cycle by clinical tumor measurements and documentation of the tumor size of measurable and nonmeasurable disease, using CT/PET scans. All sites with measurable lesions were followed for response.[18] A CR required the disappearance of all clinical and radiologic evidence of tumor. A PR required a >50% decrease in the sum of the products of the diameters of all measurable lesions. SD designated a steady-state of disease, which was a response less than a PR or progression less than progressive disease. In addition, there could be no new lesions or increases in the size of any nonmeasurable lesions for complete or partial remissions or for SD. Progressive disease indicated an unequivocal increase of at least 25% in the sum of the products of the diameters of all measurable lesions compared with baseline or the appearance of new lesions. SD was measured from the start of therapy until disease progression. The measurement of time to event variables such as duration of response for responding patients and time to progressive disease were assessed. The duration of response was calculated from the time of first objective assessment of CR/PR to the 1st time of progression or death due to any cause. The time to tumor progression was calculated from the time of study entry to the first observation of disease progression.

Statistical analysis

The descriptive statistics was done using mean or median and standard deviation or inter quartile range for quantitative variables and categorical variables presented in frequencies along with respective percentages. The statistical comparisons for quantitative variables was done using Student's *t*-test or Mann–Whitney U-test and for categorical variables Chi-square or Fisher's exact test was used as per the nature of data. All statistical analyses were performed using SPSS software (Version 16, SPSS Inc., Chicago, IL, USA). The $P < 0.05$ were considered statistically significant.

For response and progression data, two-sided 95% confidence intervals (CIs) were calculated based on an exact binomial probability at an alpha level of 0.05. Time to tumor progression was estimated using the Kaplan–Meier method. Data were analyzed using Chi-square test and Fisher's exact test, wherever appropriate. Statistical significance was defined as $P < 0.05$.

Results

Patients and treatment

310 (68.8%) patients were diagnosed as having adenocarcinoma lung between June 2013 and August 2014. Of these 310 patients 40 patients had stage II and stage III lung cancer and 87% (270) had stage IV adenocarcinoma lung. Among the 270 patients having stage IV adenocarcinoma lung, 90 were mutant for EGFR and were put on TKI, 40 patients had PS-3 (ECOG PS-3), 22 were put on chemotherapy other than pemetrexed due to unequivocal pathological and immunohistochemistry results and discretion of treating oncologist. 10 patients had dual malignancy, and so they were not included in this study. Of the remaining 108 patients who were started with induction chemotherapy of pemetrexed and platinum, 8 patients had progressive disease before completing 6 cycles of induction chemotherapy and 6 patients dropped out. 94 patients completed the intended 6 cycles of combination chemotherapy. Of these 94 patients, 30 patients were evaluated to have progressive disease after completion of 6 cycles of combination chemotherapy and 4 patients had PS-3, and hence were found to be unfit for further chemotherapy. Eventually, a total of 60 patients having non-progressive disease were put on maintenance chemotherapy of pemetrexed [Figure 1].

The median age of patients was 57 years (range: 39–72 years); median age of male patients was 60 (range: 39–72 years) and of female patients was 54 years (range: 39–71 years). 61.61% (37/60) of the patients were male and 38.33% (23/60) were female patients.

The median time from the end of induction therapy (day 21 of cycle 6) to the first maintenance dose was 3 days (range: 2–8 days), with the majority of patients (95%) initiating maintenance therapy within 7 days.

20% (n = 12) of these patients had bone metastasis, 10% (n = 6) had brain metastasis, while 70% (n = 42) had metastasis of other regions [Figure 2].

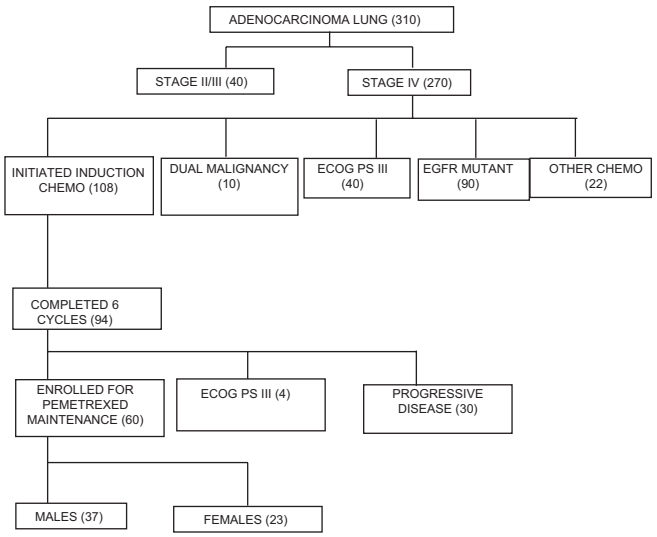

Figure 1: Selection of patients for study

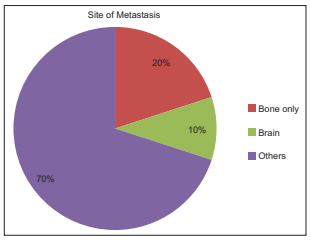

Figure 2: Proportion of patients with metastasis

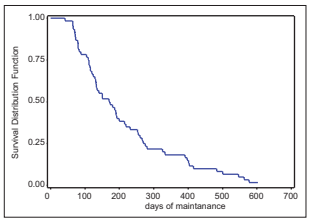

Figure 3: Kaplan–Meier plot for progression free survival shows survival probability against progression free survival given as days of maintenance

Of the 60 patients put on maintenance therapy 35% (n = 21) patients had ECOG PS status 0, 48.33% (n = 29) patients had PS-1, 16.67% (n = 10) patients had PS-2.

Patients received a median of 7 maintenance cycles and 9 as a mean number of cycles. 73.33% (n = 44) patients received more than 4 cycles, while 26.67% (n = 16) patients received 4 or less cycles of pemetrexed maintenance therapy and 51.67% (n = 31) patients received more than 6 cycles; which represents 12 total cycles of pemetrexed treatment, six cycles of induction plus six cycles of maintenance. All the patients received at least 2 cycles of chemotherapy.

Efficacy

Overall progression-free survival analysis

PFS was calculated using Log-Rank test, it was found that median PFS (in days) for all the patients was 171.50 days with 95% CI 129 days to 215 days [Figure 3].

Progression free survival analysis based on post induction response

Of the 60 nonprogressive disease patients, 29 (48.3%) had SD and 31.6%) had PR/CR on re-evaluation after 6 cycles of induction chemotherapy. Median PFS was 170 in patients with SD and 186 days for PR/CR patients [Figure 4].

Progression free survival based on sex of patients

PFS was found to be better in males than that in females with 180 and 131 days, respectively [Figure 5].

Progression free survival analysis based on best overall response

A total of 46 of the 60 patients had SD as the best overall response (BOR) on maintenance chemotherapy and 14 patients had PR. It was found that the PFS in the group with SD as BOR was 134 days while in those with PR/CR as BOR it was 267.5 days [Figure 6].

Progression free survival analysis based on metastatic site

Those patients who had metastasis in the brain had a PFS of 165 days while those with metastasis to other regions had a PFS of 171.50 days.

Progression free survival analysis based on Eastern Cooperative Oncology Group PS

PFS in those patients with ECOG PS of 0 and 1 was found to be 176.50 days, and in those with PS-2 status was found to be 136.50 days [Figure 7].

Safety analysis

To detect any adverse effect of pemetrexed maintenance therapy, safety data analysis was done from September 2013 to April 2015, 20 months. 2 patients (3.3%) in this study required the dose reduction at least in one cycle of chemotherapy due to toxicities. 4 patients (6.66%) in this study required delay in at least one cycle chemotherapy due to Grade 3 and 4 hematologic toxicities or febrile neutropenia. The median duration of the delay was 4 days (range 2–7 days). Two patient discontinued treatment because of possibly treatment-related side effects. 59/60 (98.3%) patients received more than 2 cycles of chemotherapy.

Overall fatigue was the most common adverse event in 16 patients (26.7%) with 18.3% (11/60) grade I/II and 5% (3/60) grade III/IV followed by anemia and neutropenia being the next common, 13.3% and 10%, respectively. Neutropenia was 6.66% as grade I/II and 3.33% as grade III. 14 patients had grade III/IV adverse events with anemia being the most common in 3/60 patients (5%). Fatigue and neutropenia were the next common adverse events, which were grade III/IV (5% and 3.1%, respectively). 1 patient each had grade III nausea, vomiting, diarrhea, thrombocytopenia, and renal dysfunction.

Other adverse events were < 5% and grade I/II like raised alanine transaminase/aspartate transaminase, mucositis and constipation. There were no grade 5 (death) drug-related laboratory toxicities. Comparison of the patients with longer (>6 cycles) versus shorter exposure (≤6 cycles) to pemetrexed maintenance therapy revealed no significant differences in all grades of toxicity.

Two patient discontinued treatment because of possibly treatment-related side effects. Postprogression therapy after maintenance was at the discretion of the treating oncologist. The fraction of randomly assigned patients receiving additional therapy was 91% (n = 51/56). At the time of the data cut-off, patients 4/60 (6.67% of the study population) remained on study treatment with patients still on pemetrexed.

After discontinuation of pemetrexed maintenance 35 patients were started on second-line chemotherapy, mostly docetaxel and 16 patients were put on oral TKIs (erlotinib or gefitinib). 5 patients were kept on BSC.

Discussion

Recently, pemetrexed was approved for the maintenance treatment of patients with advanced nonsquamous NSCLC who have not progressed after platinum treatment.[20] Various studies have shown the differential treatment effect (for progression-free and OS) for pemetrexed according to the histology of NSCLC.[14,21] In a phase III trial, treatment-by-histology interactions for OS and PFS were statistically significant (both $P = 0.002$) in the cisplatin plus pemetrexed versus cisplatin plus gemcitabine study, indicating that patients with nonsquamous histology who were treated with cisplatin plus pemetrexed had longer OS and PFS times than all other patients.[14] A possible mechanism for this effect could be the differential expression of thymidylate synthetase, which has been shown *in vitro* to correlate with sensitivity to pemetrexed.[22]

In the present study, the median age of the patients and sex distribution was 59 years and 61% males, respectively [Table 1], which was quiet similar to those in the paramount trial, 61 years and 59% males. 35% of the patients in this study had ECOG PS-0, again similar to paramount trial (32%) however more patients were with better PS, i.e. 44% in pronounce trial[23] and 40% in the study by Ciuleanu *et al*.[20] respectively. As per present study, 55% (60) of the 108 patients who were initially started on induction pemetrexed and platin-based chemotherapy, eventually received maintenance chemotherapy while in paramount trial 50.6% (539/939) of the induction chemotherapy patients had received maintenance pemetrexed. In the present study, 60 out of 94 (64%) patients completing induction chemotherapy did not have progressive disease (had a partial or stable response) on induction chemotherapy that was comparable to 68% in paramount trial and 61% in the study by Karayama *et al*. 51.6%. (31/60) of the nonprogressive disease patients eligible for maintenance chemotherapy in this trial had PR/CR and rest had SD as post induction response that was better as compared to 43% in the paramount trial.[24,25] More number of induction cycles in this study, 6 instead of 4 in previous maintenance trials could have resulted in better response rates in this study.

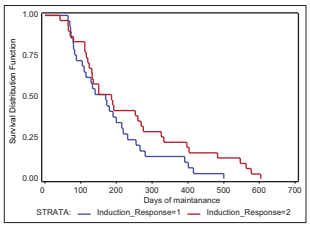

Figure 4: Kaplan–Meier plot for progression free survival shows survival probability against progression free survival given as days of maintenance in stable disease and partial response/complete response. 1 = Stable disease, 2 = Partial response/complete response

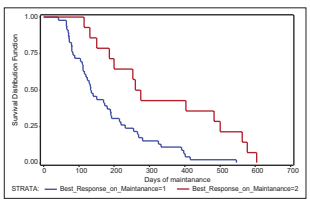

Figure 6: Kaplan–Meier plot for progression free survival shows survival probability against progression free survival given as days of maintenance for best overall response as stable disease and partial response. Best overall response: 1 = Stable disease, 2 = Partial response/complete response

In this study, it was seen that PFS was remarkable when continuous maintenance treatment with pemetrexed was given to the patients with stage IV adenocarcinoma lung after 6 cycles of combination chemotherapy. -PFS was calculated using Log-Rank test and it was found that median PFS (in days) for all the patients was 171.50 days (5.7 months) and the 95% CI for median PFS was 129 days to 215 days which was significantly better than any of the previous published trials with pemetrexed alone continuation arm, it was 4.4 months in paramount trial, 3.91 in pronounce trial, 4.4 months in study by Karayama *et al*. (continuation pemetrexed) and 4.3 months in study by Ciuleanu (switch maintenance).[20,23-25] However it was comparable to pemetrexed/carboplatin/bevacizumab arm (5.49 months) in PRONOUNCE trial.[23] PFS in patients with CR/PR as induction response was 186 and it was found to be longer than those with SD (170 days), in paramount trial also survival was numerically better in complete or partial responders though it was not a significant interaction due to possibly the SD patients in control arm fairing unexpectedly better. 23.3% (14/60) patients had PR/CR as BOR that was lesser than previous trials like a paramount trial with 44% on pemetrexed maintenance and 55% in AVAPERL trial on pemetrexed and bevacizumab maintenance.[26] However, a prominent observation from this study was that the PFS in the group with PR/CR as the BOR on continuation therapy was far better, i.e. 267.5 days, than those with constantly SD (134 days) on maintenance therapy thereby emphasizing that ongoing better response indicated a better PFS in these patients.

51% of the patients in this study received more than 4 cycles of maintenance chemotherapy as compared only 37% and 48% in previous two pemetrexed maintenance trials.[20,25] However, if we include induction therapy, a total of 10 cycles of chemotherapy were completed by an even greater number of patients in this trial (73%). Similarly, 33% of the patients in this trial completed more than 10 continuation cycles compared to 27.6% in paramount trial and again if we see total chemotherapy cycles received, 48.5% patients in this

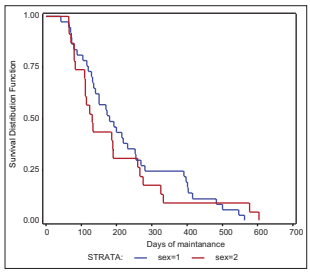

Figure 5: Kaplan–Meier plot for progression free survival shows survival probability against progression free survival given as days of maintenance for males and females (Sex: 1 = Male, 2 = Female)

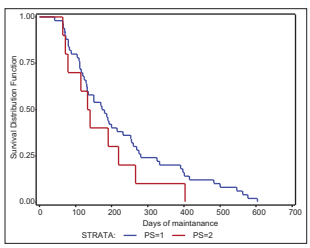

Figure 7: Kaplan–Meier plot for progression free survival shows survival probability against progression free survival given as days for plaintiff 0/l and PS-2

trial completed >14 cycles. In this trial, 6 cycles were given as combination therapy as compared to 4 cycles in previously mentioned trials, and this could have possibly resulted in the better selection of patients with responsive and biologically less aggressive disease patients among nonprogressive disease patients.

About 10% of the patients in this study had brain metastases and brain metastases were reported in 29.4% of the patients in Masato study and as in nonbrain metastases patients have marginally better PFS and a lesser number of brain metastases patients in this study could also have contributed to better PFS in this study. Moreover, no death was seen in our study during the maintenance phase, and long-term exposures were well tolerated; only 3.33% (n = 2) patients discontinued the treatment because of toxicities, which was lesser as compared to other studies with maintenance pemetrexed, 7% in pronounce trial and 12% in studies by Karayama *et al*. and Ciuleanu *et al*.

In this study, patients with SD or PR/CR following induction therapy with ECOG PS between 0 and 2 were recruited for the study, which was similar to the study population of other studies. In the present study, the patients received a median of 6 cycles of maintenance cycles and 9.8 as mean number of cycles which was more than in the PARAMOUNT study, where it was 4 and 7.9 (standard deviation, 8.3), respectively. In studies by Ciuleanu *et al*., Karayama *et al*. and PRONOUNCE trial patients had received 5 each as a median number of cycles. PFS in those patients with ECOG PS of 0 and 1 was found to be 176.50 days, which was significantly better than those with PS-2 status, in whom the PFS was found to be 136.50 days only but even this PFS in PS-2 patients was comparable that in patients with better PS in previous mentioned trials.

PFS was found to be better in males than that in females with 180 and 131 days, respectively. The reason for this difference could not be found. PFS in nonsmokers was 187.50 days and in smokers was 160 days indicating poorer treatment response and relatively aggressive disease in smokers [Table 2].

Pemetrexed was found to be safe with respect to toxicities with only 14 patients having grade III/IV side effects and 21 patients had grade I/II side effects, the incidence was similar to those of other studies with single-agent pemetrexed.

Safety analysis: To detect any adverse effect of pemetrexed maintenance therapy, safety data analysis was done over 20 months from September 2013 to April 2015. 14 patients (23.33%) had grade III/IV adverse events with anemia, fatigue and neutropenia being the most common (5%, 5% and 3.1%, respectively) among the grade I or II adverse events, anemia, nausea, and fatigue were quiet common [Table 3] but manageable, in paramount trial similar fraction of patients had higher grade of adverse events with anemia and neutropenia as most common (6.4% and 5.4%). In pronounce and Karayama *et al*. trails it was 24.3 and 20% respectively in pemetrexed arm that were also comparable to this study however in another trail by Ciuleanu *et al*. it was lesser, i.e. 16%. There were no grade 5 (death) drug-related laboratory toxicities. Comparison of the patients with longer (more than six cycles) versus shorter exposure (six or fewer cycles) to pemetrexed maintenance therapy revealed no significant differences in all grades of toxicity, all grade 3–4 drug-related laboratory toxicities, and individual grade 3–4 drug-related laboratory toxicities. However, longer exposure to pemetrexed (more than six cycles) was associated with a numeric increase in grade 3–4 neutropenia. After discontinuation of pemetrexed maintenance 90% of the patients received some sort of chemotherapy or targeted therapy (35 patients received second-line chemotherapy and 16 patients oral TKIs) while in paramount trial 83% of the patients received post pemetrexed discontinuation therapy and in pronounce trial only 43% of the patients received postpemetrexed discontinuation therapy.

In this study, there was no control arm to compare the efficacy of pemetrexed maintenance with any other chemotherapy

Table 1: Baseline characteristic of patients

Patient characteristics	Number of patients (%)
Age	57.66±8.19*; median 57 (39-72)
Sex	
Male	27 (61.6)
Female	23 (38.3)
ECOG PS	
0	21 (35.1)
1	29 (48.3)
2	10 (16.67)
Site of metastasis	
Brain	6 (10)
Bone	12 (20)
Lung and others	42 (70)
Smoking	
Smokers	30 (50)
Nonsmokers	30 (50)
Postinduction response	
SD	29 (48.3)
PR/CR	31 (51.7)

*Mean±SD wherever applicable. ECOG=Eastern Cooperative Oncology Group, PS=Performance status, SD=Standard deviation

Table 2: Median PFS according to baseline characteristic

Factor	Median PFS	95% CI	
		Lower	Upper
PFS (overall)	171.5	129	215
Postinduction status			
SD	170	104	215
PR/CR	186	124	269
Sex			
Male	180	135	253
Female	131	109	190
Smoking			
Nonsmokers	187.5	115	269
Smokers	160	129	215
Best overall response			
SD	134	111	189
PR/CR	267.5	150	500
Metastatic sites			
Brain	165	129	546
Others	171.5	120	219
ECOG PS			
PS-0, 1	176.5	129	231
PS-2	136.5	64	219

CI=Confidence interval, PFS=Progression free survival, SD=Stable disease, PR=Partial response, CR=Complete response, ECOG=Eastern Cooperative Oncology Group, PS=Performance status

Table 3: Adverse events on pemetrexed maintenance

Adverse events	Grade 1	Grade 2	Grade 3	Grade 4
Neutropenia	2	2	2	0
Fever	4	0	0	0
Anemia	3	2	2	1
Thrombocytopenia	1	0	1	0
ALT/AST	2	0	0	0
Renal dysfunction	2	0	1	0
Nausea	6	2	1	0
Vomiting	1	0	1	0
Fatigue	8	5	3	0
Diarrhea	1	1	1	0
Constipation	1	1	0	0
Hyponatremia	1	1	1	0
Edema	2	0	0	0
Mucositis	2	2	0	0

ALT=Alanine transaminase, AST=Aspartate transaminase

combination induction or maintenance. Re-evaluation was done after every 3 cycles instead of 2 cycles as done in the previously published trials so any asymptomatic progression can be detected 1 cycle later which may have also contributed to the observed PFS in this trial. The sample size was also small due to the limited time frame of study, and OS was not taken as an objective which could have better indicated the efficacy of pemetrexed maintenance.

There are very few published studies regarding outcomes of continuation maintenance pemetrexed chemotherapy in patients with metastatic adenocarcinoma India. Overall, pemetrexed maintenance chemotherapy regimen was very well tolerated in the present study. The findings of the study have significant implications for clinical practice. Clinical outcome (PFS) has been observed to be better than the similar trials reported previously, and toxicity profile of patients has been observed to be similar to that reported from the west. There is accumulating evidence now that pemetrexed as maintenance chemotherapy is safe and effective in advanced adenocarcinoma lung patients and the findings of the current study affirm that the same findings may also be extrapolated for an Indian population. The pitfall of the present study was that it included small number of patients with limited follow-up and it was nonrandomized study. Further, long-term studies and randomized trials on Indians are warranted for confirmation of these findings, bevacizumab being a costly alternative/additional option in resource-limited countries like India.

Conclusions

On the basis of experience from the present study, it can be concluded that the pemetrexed continuation maintenance chemotherapy is active and well tolerated in PS-0 to PS-2 patients with advanced adenocarcinoma lung patients. The convenience provided by the short infusion time of pemetrexed further complement the tolerability of this regimen as it can be given on outpatient basis also due to its favorable toxicity profile. The remarkable PFS of 171 days with this treatment schedule suggest further testing of pemetrexed maintenance after 4 versus 6 cycles of induction chemotherapy and also an opportunity to predict better PFS in patients with ongoing PR/CR. To the best of our knowledge, this is the first such study conducted in India. More research is required, especially in the Indian subcontinent, to assess the efficacy and tolerability of this regime in Indian patients.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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