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Prospective Analysis of Patients Treated with Chemotherapy in Metastatic Adenocarcinoma of Lung—Single Centre Experience

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Abstract

Background: Lung cancer is the leading cause of cancer-related death worldwide with an estimated 1.6 million new cases diagnosed each year. According to standard guidelines in NSCLC, the effectiveness of combined chemotherapy regimen comprises of pemetrexed and platinum, and very few reports are available in Indian population. This study shows the experience with pemetrexed and platinum combination chemotherapy in metastatic NSCLC in first line setting. **Methods:** Total 61 patients with following inclusion criteria were recruited such as: 1) PS of 1 and 2; 2) NSCLC of non-squamous histology; 3) locally advanced or metastatic disease at diagnosis; 4) should have received minimum 3 cycles of pemetrexed and platinum as first line treatment and or continued for 6 cycles; 5) EGFR/ALK mutated or EGFR/ALK unknown patients but must have received upfront chemo. Primary endpoint of the present study is to assess Disease Control Rate (DCR) (CR + PR + SD). Progression Free Survival, OS and Toxicity assessment were secondary endpoints. **Results:** The mean number of average chemotherapy cycles was found to be 4.38. The range of chemotherapy was 2 - 6 cycles. Disease control rate, defined as (CR + PR + SD), was seen in 44 (72.1%) patients. (PR in 26 (42.62%), SD 18 (29.5%)), Progressive disease (PD) was observed in 17 (27.9%) patients. Overall study showed that patients had PFS of 9.414 months (95% CI 6.709 - 12.120) and OS of 13.437 months (95% CI 10.721 - 16.153). **Conclusion:** Pemetrexed and platinum combination is effective and well-tolerated chemotherapy regimen in patients with metastatic adenocarcinoma lung cancer patients. Pemetrexed and cisplatin may be more effective in particular. Early switch over to TKIs is preferred immediately after obtaining molecular subtype result.

Keywords

Pemetrexed, Carboplatin, NSCLC, Cisplatin, EGFR

1. Introduction

Lung cancer is the leading cause of cancer-related death worldwide with an estimated 1.6 million new cases diagnosed each year [1]. Non-small cell lung cancer (NSCLC) accounts for 80% of all cases of lung cancer, and is further divided into several subgroups as adenocarcinoma, squamous cell carcinoma, large cell carcinoma, and others with 65% to 75% of them having locally advanced or metastatic disease [2]. The prognosis for advanced-stage disease remains poor, with a median overall survival (OS) of approximately a year on recent clinical trials. According to the American Society of Clinical Oncology and National Comprehensive Cancer Network (NCCN) guidelines, patients with a performance status of 0 or 1 have to be treated with a combination of 2 cytotoxic drugs in first-line therapy [3]. In patients with metastatic NSCLC of non-squamous histology, current guidelines recommend the combination of cisplatin and pemetrexed as first line induction treatment [1].

Pemetrexed is a multitargeted antifolate cytotoxic chemotherapy agent, which inhibits at least three target enzymes in the folate pathway (thymidylate synthase, dihydrofolate reductase, and glycinamide ribonucleotide formyl transferase). Consequently, pemetrexed interferes with the synthesis of both pyrimidine and purine, thereby effectively inhibiting both DNA and RNA synthesis [5]. Pemetrexed was approved in second line therapy in NSCLC based on a phase III trial comparing pemetrexed versus docetaxel. In this trial, pemetrexed showed a similar clinical activity and a lower rate of myelosuppression compared to docetaxel [4] [5]. In a secondary analysis, pemetrexed was demonstrated to be more active in non-squamous cell tumours, leading to its restriction to patients with non-squamous histology [6].

Pemetrexed and cisplatin has become the standard first line treatment regimen in metastatic NSCLC, after the first prospective analysis by Scagliotti *et al.* [7]. It showed that, patients treated with pemetrexed and cisplatin combination in advanced NSCLC, has overall survival benefit and better tolerability compared to gemcitabine and cisplatin combination. Carboplatin has less response rates but better toxicity profile and is preferred, as most of patients with advanced NSCLC have associated comorbidities. Carboplatin is non-inferior to cisplatin, if strict dose adherence is maintained [8] [9]. However, it may have inferior survival in non-squamous cancers in combination with paclitaxel, docetaxel or gemcitabine [10]. This study reports about the experience of using pemetrexed and platinum combination chemotherapy in metastatic NSCLC in first line setting.

2. Materials and Methods

Patients receiving treatment for metastatic NSCLC, followed prospectively, at Health Care Global Enterprises Ltd., Bangalore between March 2014 and December 2015.

Within the study period, 73 NSCLC patients received pemetrexed and platinum-based combination chemotherapy. Of these, 61 patients fulfilled the following inclusion criteria: 1) PS of 1 and 2; 2) NSCLC of non-squamous histology; 3) locally advanced or metastatic disease at diagnosis; 4) should have received minimum 3 cycles of pemetrexed and platinum as first line treatment and or continued for 6 cycles; 5) EGFR/ALK mutated or EGFR/ALK unknown patients but must have received upfront chemo. Patients with non-adenocarcinoma histology and EGFR/ALK mutation treated with upfront TKI were excluded. Pemetrexed 500 mg/m^2, Carboplatin (AUC5), or Cisplatin 75 mg/m^2 given once in 3 weeks. Dose adjustments made as per standard guidelines. Primary endpoint of the study was to Assess of Disease control rate (DCR − CR + PR + SD). Progression Free survival (PFS), Overall Survival (OS) and Toxicity assessment were secondary endpoints.

Statistical Analysis

PFS measured from the start date of the first pemetrexed and platinum cycle. Survival analysis performed using the Kaplain-Meier method. Spearman's rank correlation used to evaluate the relationship between performance status and number of treatment cycles.

3. Results

Of the 61 patients, receiving chemotherapy and platinum analogues, pemetrexed and carboplatin were given in 45 (73.77%) cases while pemetrexed and cisplatin was administered to 16 (26.23%) cases. The mean number of average chemotherapy cycles was 4.38. The range of chemotherapy was 2 - 6 cycles.

Following chemotherapy treatment, Disease control rate, defined as (CR + PR + SD), seen in 44 (72.1%) patients. (PR in 26 (42.62%), SD 18 (29.5%)). Progressive disease (PD) was observed in 17 (27.9%) patients. (**Figure 1**)

Responses in the molecular subtypes were as follows (**Figure 2**). The EGFR mutated patient had DCR in 14 (31.8%) patients ((PR in 9 (34.6%), SD 5 (27.8%)). and PD was seen in 2 (11.8%) patients. The EGFR wild type patient

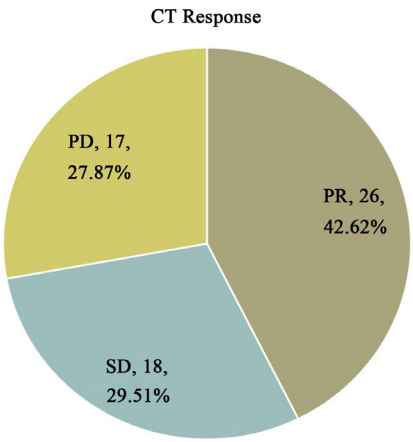

Figure 1. Response rates in study population: PR—Partial Response; SD—Stable Disease; PD—Progressive Disease.

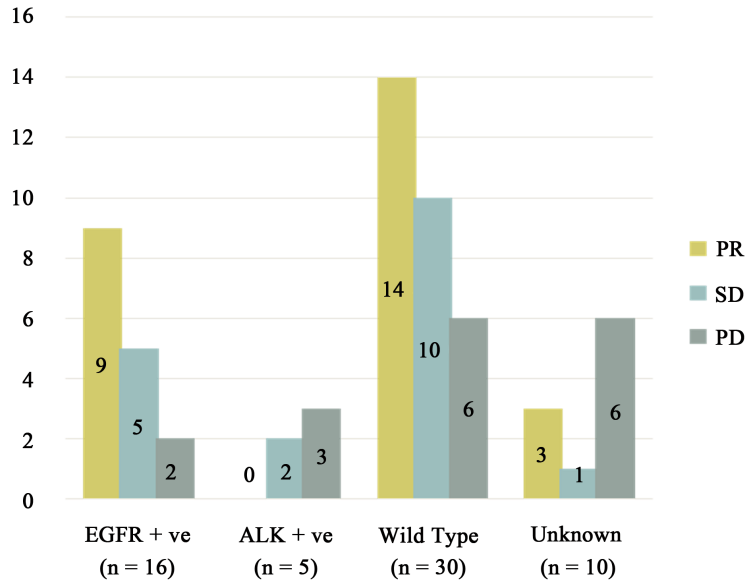

Figure 2. Chemotherapy response in molecular subtypes.

had DCR in 24 (54.5%) patients (PR in 14 (53.9%), SD 10 (35.6%)), PD was seen in 6 (15.87%). Other molecular subtype ALK mutated DCR in 2 (4.6%) patients (no PR, SD 2 (11.1%)). PD was seen in 3 (17.6%) patients. Unknown molecular status had DCR in 4 (9.1%) patients (PR in 3 (11.5%), SD 1 (5.6%)). PD was seen in 6 (35.3%) patients.

In this study, patients receiving pemetrexed plus carboplatin regimen had DCR of 30 (68.2%) (PR in 17 (65.38%), SD in 13 (72.22%)) and it was 14 (31.8%) in (PR in 9 (34.62%), SD in 5 (27.78%)) those receiving pemetrexed plus cisplatin regimen (Figure 3).

Overall study patients had PFS (Figure 4) of 9.414 months (95% CI 6.709 - 12.120) and OS (Figure 5) of 13.437 months (95% CI 10.721 - 16.153). PFS with pemetrexed and cisplatin regimen was 13 months (95% CI 7.724 - 18.501) as

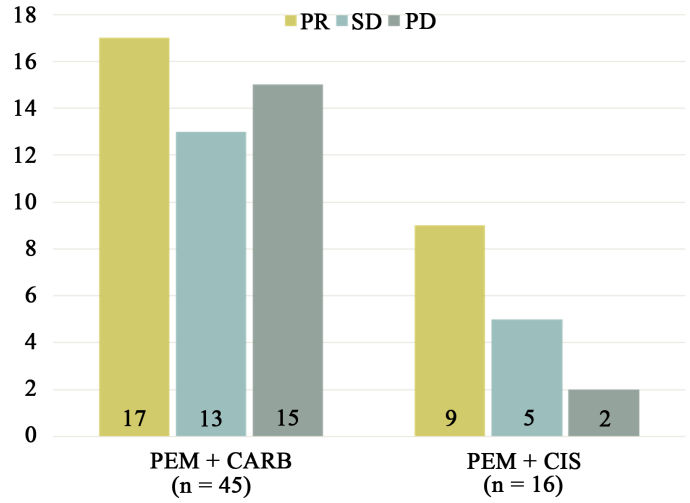

Figure 3. Response with platinum based regimen.

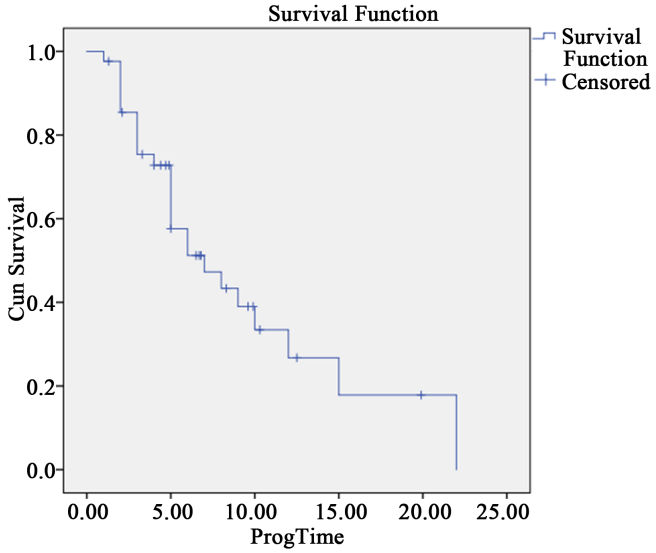

Figure 4. Kaplan-Meier progression free survival of study population.

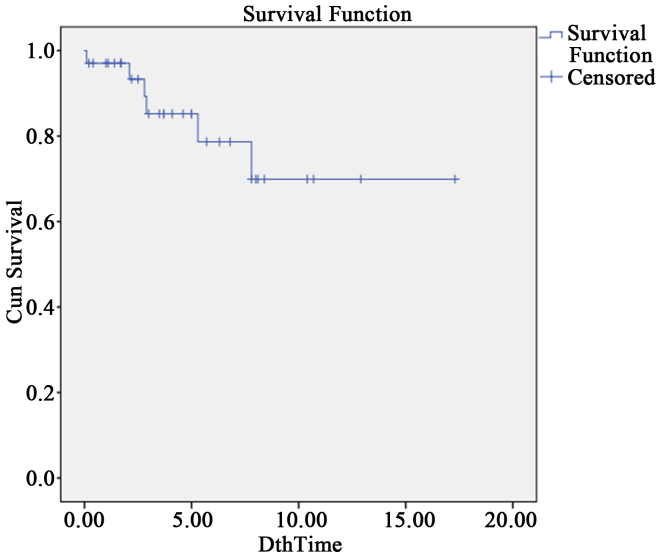

Figure 5. Kaplan-Meier overall survival of study population.

compared to 8 months (95% CI 5.217 - 10.654) with pemetrexed and carboplatin regimen ($p = 0.057$). A total number 40 (65.6%) patients tolerated chemotherapy well without any side effects. Other side effects as thrombocytopenia was seen in 11 (18%).

4. Discussion

Metastatic/Locally advanced NSCLC patients were treated with pemetrexed and platinum combination chemotherapy in first line setting. Most of the patients received average 4 cycles of chemotherapy. DCR (CR + PR + SD), of study population was seen in 44 (72.1%) patients. (PR in 26 (42.62%), SD 18 (29.5%)), There was no CR. Progressive disease (PD) was observed in 17 (27.9%) patients.

Sub type of EGFR mutated patients had lower DCR of 14 (31.8%) patients compared to EGFR wild type patients having DCR of 24 (54.5%). Overall study patients had PFS of 9.414 months and OS of 13.437 months.

Phase II study with pemetrexed and carboplatin reported PR in 12 (24%) patients and SD in 25 (50%) patients [11]. Significantly better responses observed in this study, even with the lesser dose of carboplatin (AUC5 vs. AUC 6). Phase III study reported objective response rate of 30% with pemetrexed and cisplatin [7], which is comparable to DCR of 31.8% in this study, though number of patients, were less on this regimen. As this study included EGFR mutated patients taking chemotherapy upfront also for analysis, other studies may not be comparable.

Meta-analysis by Ardizzoni A. *et al.* [9] has shown that cisplatin is superior to carboplatin. In accordance with the same, this study results have shown lesser response with cisplatin (31.8% vs. 68.2%) but higher PFS than carboplatin (13 months vs. 8 months) which was statistically significant.

Gronberg B.H. *et al.* [8] reported OS of 7.3 months compared to 13 months in this study on pemetrexed and carboplatin regimen. Survival may be more, because this study had biologically favourable EGFR mutated patients. Similarly, Scagliotti G.V. *et al.* [7] reported OS of 10 months, which is higher compared to 8 months in this study on pemetrexed and cisplatin regimen.

We had molecular subtype EGFR+ (16 patients) and ALK+ (5 patients). These patients continued on chemotherapy in view of continued clinical improvement after 1st cycle and planned to start on TKI after 4 cycles of chemotherapy. Sequist L.V. *et al.* [12] reported around 23% to 44% response rates and PFS of 6.3 months in patients with EGFR mutated patients in afatinib vs. cisplatin and pemetrexed chemotherapy trial. Same subtype of patients in this study had response rate of 31.8%, which is comparable. PFS and OS was higher (around 10 months) than the above-mentioned study. This may be the result of all patients continuing on TKIs after 4 cycle of chemotherapy.

Most of the patients 40 (65%) in present study tolerated chemotherapy well with asymptomatic grade 3 to 4 neutropenia and thrombocytopenia observed in around 20% of patients which is almost similar to other studies (7, 8) reported elsewhere.

Limitation of this study is small sample size, maintenance treatment data is not collected and inclusion of biologically favourable molecular subtype.

5. Conclusion

Pemetrexed and platinum combination is effective and well-tolerated chemotherapy regimen in patients with metastatic adenocarcinoma lung cancer patients. Pemetrexed and cisplatin may be more effective in particular. Early switch over to TKIs is preferred immediately after obtaining molecular subtype result.

Conflict of Interest

The authors declare that they have no conflict of interest.

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