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Original Article

Efficacy and Toxicity Profile of Various Second-line Chemotherapeutic Drugs in Stage III and Stage IV Non-small Cell Lung Cancer

R Deivanayagam

Associate Professor, Department of Radiotherapy, Tirunelveli Medical College and Hospital, Tirunelveli, Tamil Nadu, India

Abstract

Introduction: The majority of patients with non-small cell lung cancer (NSCLC) present with advanced stage disease – Stage IV, in particular, and half of the patients treated initially for the potentially curable early-stage disease will recur with metastatic disease. This is true even in developed countries. Patients with Stage IV disease are never curable, and chemotherapy, targeted therapy, and radiation can extend survival and palliate symptoms.

Aim: The aim of this study was to assess the clinical efficacy of various drug regimens used as the second-line chemotherapy in NSCLC and to assess the various toxicity profile of the second-line therapeutic agents used in NSCLC.

Materials and Methods: Patients with locally advanced non-small cell lung cancer exposed to first-line chemotherapy were selected for one of the second-line treatment regimens (carboplatin + gemcitabine, carboplatin + pemetrexed, docetaxel, gemcitabine, and gefitinib) based on age, performance status (PS), and histopathology. All regimens were planned for a maximum of 4 cycles except gefitinib which was given until progression. The response was assessed by computed tomography chest scan using response evaluation criteria in solid tumor criteria 1.1 and toxicity was assessed using common terminology criteria for adverse events 4.03.

Results: Of 50 patients, nine patients received carboplatin/gemcitabine, 14 patients received carboplatin/pemetrexed, 11 patients received docetaxel, 10 patients received gemcitabine, and 6 patients received gefitinib. Of five arms, patients who had docetaxel showed an improvement in Eastern Cooperative Oncology Group (ECOG) PS, but the observation was not statistically significant. This study had observed that none of the second-line regimens were superior to others, but patients who received docetaxel had shown improvement in ECOG PS.

Conclusion: In NSCLC patients who progressed on first-line chemotherapy, all five regimens used in the study were equally efficacious.

Key words: Chemotherapy, Non-small cell lung cancer, Stages III–IV

INTRODUCTION

Carcinoma lung is the most common malignancy among men and the most common cause of death related to malignancy in both the sexes. In our center, it is the most common malignancy encountered among males accounting for about 11.6% of cases. Most of them present with advanced and metastatic stage needing palliative chemotherapy. Although various drugs have been tried, platinum remains a cornerstone in the management. Non-small cell lung carcinoma is the most common and squamous cell carcinoma being more common in males, whereas adenocarcinoma is more common in females.[1,2] With the advent of tyrosine kinase inhibitors, the outlook of non-small cell lung cancer (NSCLC) has changed. Erlotinib and gefitinib are used for a patient with epidermal growth factor receptor (EGFR)-mutated lung cancer, whereas crizotinib is used for anaplastic lymphoma kinase (ALK)-rearranged lung malignancies. For patients who had completed first-line platinum-containing

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Corresponding Author: Dr. R Deivanayagam, Department of Radiotherapy, Tirunelveli Medical College and Hospital, Tirunelveli, Tamil Nadu, India

agents, gemcitabine has been used in the subsequent lines. Docetaxel was mostly used in the palliative setting as a single agent in a promising agent with a median survival of 5–6 months. According to paramount trial, pemetrexed can be used for continuation maintenance, but pemetrexed is an expensive drug and, therefore, is a need for the cost-effective drug as a salvage agent in the resource-poor setting. Our study will find the usefulness of these agents in the salvage setting for the treatment of advanced and metastatic NSCLC.[3,4] Chemotherapy for advanced lung cancer is known to improve survival and quality of life compared with symptomatic treatment. Lung cancer usually progresses after chemotherapy. Second-line chemotherapy allows improved survival rate compared with patients given symptomatic treatment. There are three agents such as docetaxel, pemetrexed, and erlotinib which are approved as second-line drugs in NSCLC. The choice of drug depends on the patient's comorbidities, toxicity from previous treatment, smoking history, and patient preference. In general, the median survival was 9 months in patients with good performance status (PS).[5,6]

Aim

The aim of this study was to assess the clinical efficacy of various drug regimens used as the second-line chemotherapy in NSCLC and to assess the various toxicity profiles of the second-line therapeutic agents used in NSCLC.

MATERIALS AND METHODS

This prospective observational study was conducted in the Department of Medical Oncology at Madras Medical College. 50 patients who had registered in the outpatients from July 2015 to February 2016 as NSCLC (adenocarcinoma and squamous cell carcinoma) with advanced stage (Stages III and IV), who had progressed on first-line chemotherapy, were selected for one of the second-line treatment regimens (carboplatin + gemcitabine, carboplatin + pemetrexed, docetaxel, gemcitabine, and gefitinib) based on age, PS, and histopathology. Routine investigations were done before starting chemotherapy. Cardiology fitness was obtained before starting chemotherapy.

Inclusion Criteria

Patients with locally advanced NSCLC, patients with age – 18–65 years, patients with PS by the Eastern Cooperative Oncology Group (ECOG) 1–3, and patients who had exposed to first-line chemotherapy drugs were included in the study.

Exclusion Criteria

PS by ECOG 4 exposed to multiple lines of treatment.

- Regimen 1: Carboplatin + Gemcitabine – 9 patients were recruited
- Regimen 2: Carboplatin+ Pemetrexed – 14 patients were recruited
- Regimen 3: Docetaxel – 11 patients were recruited
- Regimen 4: Gemcitabine – 10 patients were recruited
- Regimen 5: Gefitinib – 6 patients were recruited.

All regimens were planned for a maximum of 4 cycles except gefitinib which was given until progression. The response was assessed by computed tomography chest scan using response evaluation criteria in solid tumor criteria 1.1 and toxicity was assessed using common terminology criteria for adverse events 4.03. The study was conducted after approval from the institutional ethical committee and in accordance with their regulations. Informed consent was obtained, after explaining the study details, from all patients, before enrolment.

Descriptive methods were used to analyze baseline characteristics. The intention to treat population was used to analyze the efficacy and toxicity of chemotherapy regimens. Chi-square test and Pearson Chi-square test were used to establish the significance.

RESULTS

In this study, 50 patients with advanced lung cancer were enrolled. Nine patients were treated with carboplatin and gemcitabine, 8 of the patients (89%) were male, and one patient is female. Mean age in the subgroup was 50 years. All the patients had squamous cell carcinoma. Seven patients in the subgroup (78%) were ex-smokers and two (22%) of them were current smokers. Seven patients had Stage III B and two patients had Stage IV disease.

In the 2nd subgroup, fourteen patients were enrolled to receive carboplatin and pemetrexed. Mean age was 52 years. All the patients had adenocarcinoma. In this cohort, 9 (64%) patients were males, and patients were females (36%). 57% of them were in Stage III and 43% in Stage IV, and of the 14 patients, 57% (8) were current smokers, 7% (1) were ex-smoker, and 36% (5) were never smokers. All the females in this subgroup are nonsmokers.

In the 3rd subgroup, 11 patients were treated with docetaxel. In this subgroup, 64% (7) were males and 36% (4) were females. In this cohort, 64% had Stage III disease and 36% had Stage IV disease. One patient had squamous cell carcinoma and 10 patients had adenocarcinoma. Of the 11, 46% (5) were non-smokers and 27% (3) each were current and non-smokers.

In the single-agent gemcitabine arm, a total of 10 patients were enrolled, 70% (7) of patients were males and 30% (3) were females. Mean age of the patients was 55 years. In the

Table 1: Demographic characteristic of the study

Group	Median age	Male sex	Female sex	Stage III	Stage IV	Histology
I	50	8	1	7	2	All squamous
II	52	9	5	8	6	All adenocarcinoma
III	53	7	4	7	4	One - squamous 10 - adenocarcinoma
IV	55	7	3	-	10	All adenocarcinoma
V	52	4	2	-	6	All adenocarcinoma

Table 2: Hematological toxicities of different regimens

Regimens	Anemia - G3/4	Neutropenia - G3/4	Thrombocytopenia - G3/4
Carboplatin/gemcitabine	7/9	7/9	7/9
Carboplatin/pemetrexed	10/14	10/14	10/14
Docetaxel	4/11	4/11	4/11
Gemcitabine	2/10	2/10	2/10
Gefitinib	0/6	0/6	0/6

Table 3: Hematological toxicity in the cohort

Regimen	Anemia	Neutropenia	Neutropenia 2	Total
Carboplatin/ gemcitabine	7	7	7	9
Carboplatin/ pemetrexed	10	10	10	14
Docetaxel	4	4	4	11
Gemcitabine	2	2	2	10
Gefitinib	0	0	0	6

cohort, 50% (5) were non-smokers, 30% (3) were current smokers, and 20% (2) were ex-smokers. All patients were in Stage IV. All the patients had adenocarcinoma as histology. In this subgroup, 50% (3) of patients were ex-smokers, 33% (2) were never smokers, and 17% (1) were current smokers.

In gefitinib arm, six patients were enrolled. Mean age of the patients were 52 years.

Of 6, four patients males were (67%) and two were females (33%) [Table 1].

Toxicity in terms of CTC-AE was measured during every cycle visit and is tabulated in Table 2.

Patients who had doublet chemotherapy with carboplatin/ gemcitabine and carboplatin/pemetrexed had more incidence of grade 3 and 4 hematological toxicity. In the carboplatin/gemcitabine arm, 77% of the patients had grade 3/4 anemia, neutropenia, and thrombocytopenia. In the carboplatin/pemetrexed arm, 72% had grade 3 and 4 hematological toxicity. Patients who had doublet chemotherapy received more growth factor support when compared to single agents such as docetaxel (36%), gemcitabine (20%), and gefitinib (0%). The occurrence of hematological toxicity in the doublet arm was statistically significant ($P < 0.05$) [Tables 3 and 4].

Regarding non-hematological toxicities, the doublet arm had more incidence of constipation (carboplatin/gemcitabine – 33% and carboplatin/pemetrexed – 36%). Fatigue was the only non-hematological toxicity seen all the arms of second-line chemotherapy. Fatigue had a 100% association with EGFR inhibitor gefitinib. Patients who had carboplatin/ pemetrexed (64%) and gefitinib (84%) had more incidence of vomiting when compared to other arms. Barring single-agent gemcitabine, all the other arms had a significant incidence of mucositis. Patients who had gefitinib had 50% incidence, and other arms such as carboplatin/gemcitabine, carboplatin/ pemetrexed, and docetaxel had an incidence between 35% and 45%. Patients who had gefitinib had more incidence of diarrhea when compared to other arms (50%). Neuropathy as in expected line was common in pemetrexed arm (42%). Rash was the most common in patients who had gefitinib, and around 50% of patients under gefitinib arm suffered from the rash. Alopecia was observed in all, except in gefitinib arm. Patients who had carboplatin/pemetrexed experienced more incidence of alopecia (42%) [Tables 5 and 6].

At the end of 7 months, patients who had docetaxel had shown improvement in PS (from ECOG PS 2 to ECOG PS 0) when compared to other four regimens in the study group. This observation is statistically significant.

In Figure 1, the progression-free survival (PFS) and PS were plotted against various chemotherapy regimens. It is seen that patients who had docetaxel had an improvement in PFS (more patients are in ECOG PS 1 and 2) compared to the doublet arms [Table 7, Figures 2 and 3].

The median PFS for patients who had chemotherapy was almost similar in all the arms. PFS was marginally high in the docetaxel arm, but the difference was not statistically significant ($P = 0.189$).

Table 4: Non-hematological toxicity of different regimens

Regimen	Constipation	Fatigue	Vomiting	Mucositis	Diarrhea	Neuropathy	Rash	Alopecia
Carboplatin/gemcitabine	3/9	6/9	4/9	4/9	2/9	0/9	0/9	3/9
Carboplatin/pemetrexed	5/14	10/14	9/14	6/14	0/14	6/14	1/14	6/14
Docetaxel	0/11	4/11	1/11	4/11	0/11	1/11	2/11	4/11
Gemcitabine	1/10	5/10	1/10	0/10	3/10	1/10	0/10	4/10
Gefitinib	0/6	6/6	5/6	3/6	3/6	0/6	3/6	0/6

Table 5: Distribution of non-hematological toxicity in the cohort

Regimen	Constipation	Fatigue	Vomiting	Mucositis	Diarrhea	Neuropathy	Rash	Alopecia
Carboplatin/gemcitabine	3	6	4	4	2	0	0	3
Carboplatin/pemetrexed	5	10	9	6	0	6	1	6
Docetaxel	0	4	1	4	0	1	2	4
Gemcitabine	1	5	1	0	3	1	0	4
Gefitinib	0	6	5	4	4	0	3	0

Table 6: PS comparison

Regimen	PS				*P* value
	1	2	3	5	
Carboplatin/gemcitabine	0	4	2	3	0.01
Carboplatin/pemetrexed	4	3	1	7	
Docetaxel	5	3	0	2	
Gemcitabine	0	1	5	4	
Gefitinib	0	0	3	3	

PS: Performance status

Table 7: PFS

Regimen	PS						*P* value
	2	3	4	5	6	7	
Carboplatin/gemcitabine	0	0	1	5	2	1	0.189
Carboplatin/pemetrexed	0	4	5	3	2	1	
Docetaxel	0	1	3	2	3	1	
Gemcitabine	0	3	3	2	1	1	
Gefitinib	2	1	1	1	1	0	

PFS: Progression-free survival, PS: Performance status

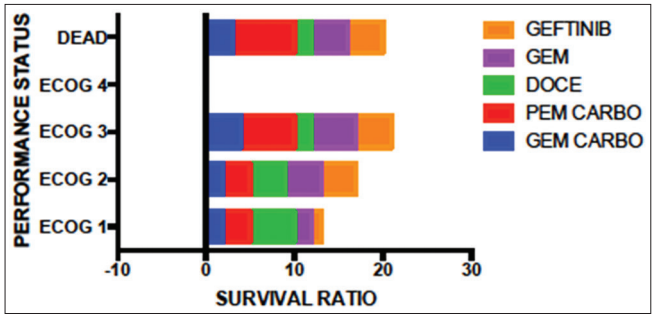

Figure 1: Distribution of survival ratio

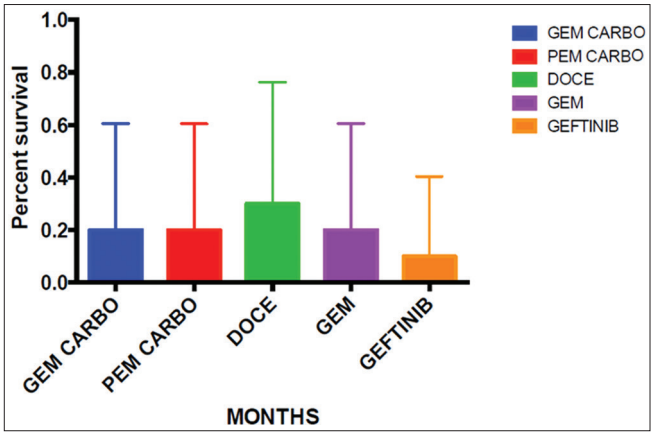

Figure 2: Distribution of progression-free survival

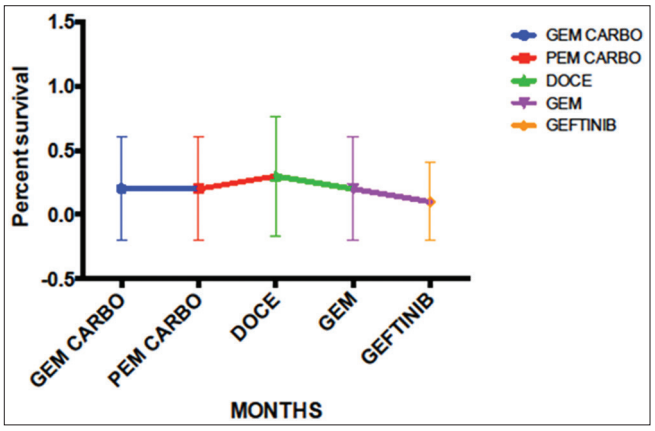

Figure 3: Comparison of median plot

DISCUSSION

For patients with advanced NSCLC with negative or unknown EGFR/ALK status and adequate PS, when disease has progressed during or after first-line platinum-based therapy, docetaxel, erlotinib, gefitinib, gemcitabine, or pemetrexed is acceptable second-line therapy either as single agent or in combination with platinum agents according to the ASCO Clinical Practice Guideline Update, 2015. Accordingly, five regimens were selected for testing in this clinical trial.

The median PFS for carboplatin/gemcitabine arm in this study was 5 months. In a study by Arrieta *et al.*, who compared carboplatin/gemcitabine with carboplatin/pemetrexed in 23 patients experiencing progression following 6 months after concluding platinum-based chemotherapy. This study included patients who had progression after 6 months of platinum-based first-line chemotherapy and this may explain the better PFS observed in this study. The study group in the cohort had progression within 6 months of platinum-based chemotherapy. The toxicity profile observed in the Arietta *et al.* was similar to that of observed in this study. The incidence of hematological toxicity in the study was 77%, and fatigue was the most common non-hematological toxicity seen in 72% of patients.[7]

In the carboplatin/pemetrexed arm, the median PFS was 4 months. In a study by Ardizzoni *et al.* (NAVLT7 – TRIAL) comparing carboplatin/pemetrexed with single-agent pemetrexed in 239 patients who had progressed after first-line chemotherapy, the author had observed no statistical difference between the two arms with regard to PFS. The median PFS observed in the study was 3.5 months for both the arms. This result was in accordance with our trial which had 4 months as median PFS. Regarding toxicity profile, the incidence of hematological toxicity was more common, 72% of the patients had grade III/IV hematological toxicity, and most of them need growth factor support for recovery. The most observed hematological toxicity in NAVLT7 trial was neutropenia seen in 12% of patients.[8]

The docetaxel arm had shown a PFS of 5 months. There were three landmark trials which had shown the effectiveness of docetaxel as second-line chemotherapy in patients with advanced lung cancer in first of the trial TAX 317; the authors had compared single-agent docetaxel with that of best supportive care (BSC) in patients who had progressed under first-line chemotherapy. The observed PFS in TAX 317 trial was 3.6 as opposed to 4.5 months in this study. However, small phase II trial by Takeda *et al.* and Yıldırım *et al.* had shown PFS as high as 4.1 months and 5 months, respectively, which is in accordance with this study. Regarding hematological toxicity in TAX 317 trial, the incidence of anemia was 5.6% and neutropenia in all grades was 67%, and in this study, the observed incidence of anemia was 35% and neutropenia grade III/IV was 36% which is in accordance with TAX 317 and TAX 320 trials. The more incidence of anemia in this population can be explained by multifactorial etiology.[9,10]

Patients who had single agent gemcitabine had a median pfs of 4.5 months. According to Yıldırım *et al.* who had compared single-agent gemcitabine with docetaxel, the author had observed a median PFS of 5 months in both the arms. This observation is in accordance with this study. The major hematological toxicity observed in this study was neutropenia and anemia seen in 20% of the patients. The study by Yıldırım *et al.* had not observed any hematological toxicity. Overall, there was 47% incidence of non-hematological toxicity in the study by Yıldırım *et al.*, and the most common non-hematological toxicity observed in this study was fatigue seen in 50% of patients followed by alopecia seen in four patients.[10]

The benefit of gefitinib as a single agent modality for adenocarcinoma patients who failed first-line treatment was proven by two randomized trials – IRESSA and SIGN trial. The IRESSA study was a negative trial which had not shown any overall survival benefit when compared with BSC. The results had been attributed to selection bias in this study. The observed PFS in this study was 3 months which is akin to SIGN and IRESSA trials. The observed toxicity in this trial was similar to that of observed in SIGN trail, skin rash was seen in 50% of patients in this study, and diarrhea was seen in 3 patients.[11]

Overall while comparing different second-line regimens, there was no superiority of one regimen over the other. A meta-analysis by Di Maio *et al.* which included 8 trials and compared doublet versus single agent as second-line chemotherapy in advanced lung cancer had shown that there was no OS benefit while comparing single-agent versus doublet. However, the doublet arm had a 45% incidence of hematological toxicity as compared to 25% in single agent regimens. The grade III and IV non-hematological toxicity was not statistically significant between the regimens. In this study, the median PFS was not statistically significant between the regimens. The doublet arm had more hematological toxicity when compared to single-agent regimens. Patients who had docetaxel had better PFS (5 months) and favorable toxicity profile and better ease of administration. Patients who had docetaxel as second-line palliation had improvement in ECOG PS from 2 to 1 or 0. Although single-agent gemcitabine had less incidence of overall toxicity and median PFS of 4.5 months, the ease of administration was better with docetaxel (every 3 weeks vs. weekly gemcitabine for 3 weeks every 4 weeks).[12]

CONCLUSION

The PFS was approximately 4.5 months in all groups. It was marginally higher in the docetaxel arm (5 months), but the difference was not statistically significant. The toxicity profile was of tolerable and acceptable levels across all arms of second-line palliative chemotherapy. Toxicity was even lesser when single-agent chemotherapy

was used. In NSCLC patients who progressed on first-line chemotherapy, all five regimens used in the study were equally efficacious. In NSCLC patients who progressed on first-line palliative chemotherapy, the most important determinants of outcome were preserved PS.

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