Efficacy and safety of pemetrexed and cisplatin chemotherapy as first line in advanced stage of lung adenocarcinoma.

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Abstract

Background: Pemetrexed is a newer antifolate drug that has multiple intracellular targets. Clinical trials of Pemetrexed in advanced nonsmall cell lung carcinoma (NSCLC) setting have demonstrated beneficial outcomes. This study evaluated the efficacy and safety of Pemetrexed and Cisplatin combination as first line in advanced stage NSCLC adenocarcinoma patients.

Methods: This was a prospective study conducted on previously untreated 50 patients with NSCLC (adenocarcinoma) of stage III B and IV disease. Patients received Pemetrexed 500 mg/m^2 and Cisplatin 75 mg/m^2 on day 1 of every 21-day cycle for a total of 6 cycles. Tumor response was calculated after 3 cycles and 6 cycles as per RECIST criteria version 1.1. Toxicity and adverse events (AEs) were assessed as per Common Terminology Criteria for Adverse Events (CTCAE) version 3.

Results: The tumor response rate after 6 cycles of chemotherapy was as follows: 12% (6) patients had complete response, 48% (24) had a partial response, and 22% (11) stable disease. The overall response rate was 60% and the clinical benefit rate was 82%. Out of total patients, hematological toxicity in the form grade 3/4 granulocytopenia was seen in 20 (40%) patients, followed grade 3/4 leukopenia 12 (24%), grade 3/4 anaemia in 5 (10%) and grade 3/4 thrombocytopenia in 5(10%). Whereas non-hematological toxicity was comparatively less in the form of grade 3 vomiting in 2 (4%) patients. Over all this combination was well tolerated.

Conclusion: Pemetrexed and Cisplatin chemotherapy combination was found to be efficacious and was well tolerated in advanced NSCLC adenocarcinoma patients.

Keywords: Pemetrexed, Cisplatin, Lung carcinoma, Non-small cell, NSCLC.

Accepted on September 26, 2018

Introduction

Lung cancer is the leading cause of cancer death among males in both developed and developing countries. Based on GLOBOCAN estimates, about 14.1 million new cancer cases and 8.2 million deaths occurred in 2012 worldwide [1]. In India, there is a significant rise in the burden of lung cancer. Smoking tobacco, both cigarettes and beedis, is the principal risk factor for causation of lung cancer in Indian men. There is a shifting histo-pathological pattern with rise in the incidence of adenocarcinomas. Non-small cell lung cancer (NSCLC) are the major subtype of lung cancers [2]. In advanced-stage NSCLC, doublet combinations with platinum compounds are standard regimens, with Cisplatin being the cornerstone of most regimens [3,4].

Pemetrexed is a newer antifolate drug that has multiple intracellular targets. It inhibits several enzymes of the folate pathways, including thymidyiate synthase, dihydrofolate reductase, and glycinamide ribonucleotide formyl transferase [5]. Phase II and III clinical trials have assessed the efficacy and safety of pemetrexed with cisplatin for first-line treatment of advanced NSCLC [6-10].

Results of few trials have shown that, the combination of pemetrexed with cisplatin tended to be more effective in nonsquamous histology subtypes than squamous cell, in terms of response rate and survival outcomes [10,11]. Scagliotti et al. in a phase III trial showed that the combination of cisplatin and pemetrexed was not inferior to cisplatin and gemcitabine combination in advanced NSCLC. Further subgroup analysis of the trial based on histologic type demonstrated that, cisplatin and pemetrexed in patients with adenocarcinoma resulted in significantly better survival than cisplatin and gemcitabine [10]. There exists paucity of evidence in Indian literature. Therefore, the present study was conducted to assess the efficacy and safety of Pemetrexed and Cisplatin combination as first line in advanced NSCLC adenocarcinoma patients.

Material and methods

This was a prospective, single arm; interventional study carried out in patients with advanced NSCLC, attending Department of Medical Oncology at Bhagwan Mahaveer Cancer Hospital and Research Centre (BMCHRC), Jaipur (India) during May 2011-December 2011. The sample size was set to 50 patients based on previous studies. The study was approved by the Institutional Ethical Committee and was conducted in

accordance with Good Clinical Practice (GCP) guidelines and the Declaration of Helsinki.

The study included previously untreated patients with the following eligibility criteria: 1) Histologic or cytologic diagnosis of NSCLC (adenocarcinoma) of stage III B and IV disease, 2) Age 18–70 years, 3) Performance status (0-2), 4) normal hematological and biochemical parameters (renal, hepatic & bone marrow reserve) and 5) Estimated life expectancy of at least 3 months.

The study excluded the following patients: 1) Histologic diagnosis of squamous cell carcinoma , 2) Age <18 years and >70 years, 3) Prior systemic chemotherapy, chemotherapy for pleurodesis, immunotherapy, or biological therapy, 4) Inadequate hematologic, cardiac, renal and hepatic functions, 5) History of allergy with similar biological to Pemetrexed/ Cisplatin, 6) Symptomatic brain metastases, 7) Any second primary malignancy (except *in situ* carcinoma of the cervix or adequately treated non melanomatous carcinoma of the skin or other malignancy treated at least 5 years previously with no evidence of recurrence, 8) Active/Uncontrolled infection/any other severe systemic diseases, 9) Patients not willing for informed consent, and 10) Pregnant and lactating females.

All patients underwent detailed history, physical examination, a complete blood cell count (CBC) and blood biochemistry, an electrocardiogram, viral markers including HIV and Hepatitis B, radiologic imaging study including, chest X-rays, CECT Thorax, Bone scan and USG Abdomen were done as a part of metastatic work up.

Drugs administration

Patients were administered IV Pemetrexed 500 mg/m^2 as an IV infusion in 0.9% normal saline (100 ml) within 10 minutes on day 1 of every 21-day cycle and IV Cisplatin 75 mg/m^2 IV infusion in 0.9% normal saline (250 ml) over 2 hours starting 30 minutes after Pemetrexed administration, on day 1 of every 21-day cycle for a total of 6 cycles along with proper premedication and post-medication.

Premedication and post medication included 5HT3 antagonist-Granisetron (1 mg bolus 15 minutes before chemotherapy), Dexamethasone (4 mg BD with food) on the day prior, same day and following Pemetrexed administration, Aprepitant (125 mg 1 hour before chemotherapy on day 1, 80 mg on day 2 and 3 in the morning), proton pump inhibitor, IV fluids (0.9% normal saline: 1-2 litres before and 1 litre after Cisplatin infusion), IV furosemide after Cisplatin infusion, IV Mannitol 10% (250 ml) over 15 minutes 30 minutes before and after Cisplatin infusion, 20 meq potassium chloride and 2 ampoules Magnesium sulphate in 0.9% normal saline). Oral Folic acid (350-1000 µg) and a Vitamin B12 injection (1000 µg) given intramuscularly (1 week before Pemetrexed injection and continued 3 weeks after the last dose of study treatment) were also administered. Patients were assessed weekly for symptomatic, clinical improvement and adverse reactions in each cycle. Patients were evaluated after 3 cycles & 6 cycles and at follow-up visits.

Parameters evaluated

Tumor response Assessment: The tumor response was evaluated after 3 cycles and 6 cycles of combination chemotherapy using the Response Evaluation Criteria in Solid Tumors (RECIST version 1.1) criteria [12]. The response outcomes evaluated were complete response (CR), partial response (PR), progression of disease (PD), and stable disease (SD).

Toxicity assessment: Adverse events (AEs) and treatment related toxicities were assessed and graded as per Common Terminology Criteria for Adverse Events (CTCAE) version 3 [13].

Statistical analysis

Analysis was performed with SPSS, version 20. Descriptive statistics was used to express the data. For categorical variables, Chi square/Fischer exact test were used as appropriate. P values $\leq$ 0.05 was considered statistically significant.

Results

A total of 50 patients with NSCLC (adenocarcinoma) of stage III B and IV disease were enrolled in this study.

Baseline characteristics

Out of the total 50 patients, 37 were males (74%) and 13 were females (26%). Male to female ratio was 2.8:1. The mean age in males was 52.94 years and in females was 52.23 years. Majority patients were smokers (n=37, 74%). Thirty three (66%) patients had right lung carcinoma, while 17 (34%) had left lung carcinoma. Majority patients (n=38, 76%) had stage IV disease and a good performance status 0-1 (n=31, 62%). The baseline characteristics of advanced NSCLC (adenocarcinoma) patients are depicted in Table 1.

Efficacy outcomes

Tumor response: The tumor response rate after 3 cycles of chemotherapy was as follows: 4% (2) patients had complete response, 72 % (36) had partial response, 18% (9) stable disease and 6% (3) progressive disease. The objective response rate and clinical benefit rate achieved was 76% (38) and 94% (47) respectively (Table 2).

The tumor response rate after 6 cycles of chemotherapy was as follows: 12% (6) patients had complete response, 48% (24) had partial response, 22% (11) stable disease and 18% (9) progressive disease. The objective response rate and clinical benefit rate achieved was 60% (30) and 82% (41) respectively (Table 3).

Compliance with treatment

Safety and toxicity: Hematological toxicity was more as compared to non-hematological toxicity. In total, grade 3 and 4 hematological toxicity was seen in 32 patients (64%) and 11 patients (22%) respectively. Whereas, the grade 3 and 4 non-

hematological toxicity was seen in 5 (10%) patients and 1 (2%) patient (Table 4).

The most common hematological toxicity encountered with the combination chemotherapy was granulocytopenia, followed by leukopenia. While in non-hematological toxicity, gastrointestinal-related toxicities were commonly encountered (Table 4). Biochemical derangement was seen in few patients. Increased creatinine (grade 1/2), SGOT and SGPT (grade 3) and bilirubin (grade 2) was seen in 2 (4%), 1 (2%) and 1 (2%) patient respectively (Table 5).

Table 1: *Baseline characteristics of NSCLC (adenocarcinoma) patients.*

Characteristics		**Value**	**%**
Total patients of NSCLC -adenocarcinoma		50	100
Patient Characteristics			
Age in years	Mean	52.58	
Age group in years	<60	34	68
	≥ 60	16	32
Gender	Male	37	74
	Female	13	26
Performance status	0-1	31	62
	2	19	38
Smoker	Yes	37	74
	No	13	26
Tumour characteristics			
Anatomical side	Right lung	33	66
	Left lung	17	34
Tumour Stage	III	12	24
	IVA	38	76
Number of Metastatic sites	0	11	22
	1	21	42
	2	15	30
	3	2	4

Table 2: *Tumor response after 3 cycles with Pemetrexed and Cisplatin combination chemotherapy*

S.no	**Tumour response after 3 cycles**	**Tumour Stage**		**Total patients=50 n (%)**
		III B	IV	
1	Complete response (CR)	0	2	02 (4%)
2	Partial response (PR)	10	26	36 (72%)
3	Stable disease (SD)	2	7	09 (18%)
4	Progressive Disease (PD)	0	3	03 (6%)
5	Objective response rate (CR +PR)	10	28	38 (76%)
6	Clinical response rate (CR +PR+SD)	12	35	47 (94%)

Table 3: *Tumor response after 6 cycles with Pemetrexed and Cisplatin combination chemotherapy.*

S. no	**Tumour response after 6 cycles**	**Tumour Stage**		**Total patients=50 n (%)**
		III B	IV	
1	Complete response (CR)	2	4	06 (12%)
2	Partial response (PR)	7	17	24 (48%)
3	Stable disease (SD)	3	8	11 (22%)
4	Progressive Disease (PD)	0	9	09 (18%)
5	Objective response rate (CR+PR)	9	21	30 (60%)
6	Clinical response rate (CR +PR+SD)	12	29	41 (82%)

Discussion

The findings of the present study indicate that Pemetrexed and cisplatin combination chemotherapy was active and well tolerated in patients with advanced NSCLC (adenocarcinoma).

The last decade has seen the introduction of several new chemotherapeutic agents that have activity against NSCLC and that produce single agent response rates of greater than or equal to 20% in previously untreated patients with advanced tumors. Response rates for the new agents in combination with cisplatin or carboplatin, have 35% to 40% [14].

Pemetrexed belongs to the 'folate antimetabolites' class of chemotherapy drugs. It is distinctive amongst the antimetabolites in that it is multitargeted, this characteristic may translate to possible advantages in terms of broad spectrum anticancer activity, resistance and potency [15]. Pemetrexed is polyglutamated intracellularly by folylpolyglutamate synthetase (FPGS) that is essential for its antiproliferative activity. Pemetrexed and its polyglutamate derivatives mainly inhibit three key enzymes of intracellular `folate metabolism, critical for purine and pyrimidine synthesis- thymidylate synthase (TYMS), dihydrofolate reductase (DHFR) and glycinamide ribonucleotide formyltransferase (GARFT), with TYMS being the most relevant target [5]. This feature of multitargeted, distinguishes it from the older generation of antifolates.

Pemetrexed has demonstrated good efficacy and tolerability profile in combination with cisplatin in advanced NSCLC especially in nonsquamous subtype [6-11,16]. Based upon the promising outcomes documented in nonsquamous NSCLC [10,11] the present study evaluated the efficacy and safety of Pemetrexed and Cisplatin combination in advanced NSCLC adenocarcinoma patients in India.

Table 4: *Hematologic and Non-Hematologic Toxicities with Pemetrexed and Cisplatin combination chemotherapy.*

Toxicities	Grade (N=50)			
	Grade 1, n (%)	Grade 2, n (%)	Grade 3, n (%)	Grade 4, n (%)
Hematologic				
Anemia	3 (6.0)	1 (2.0)	4 (8.0)	1 (2.0)
Leukopenia	1 (2.0)	2 (4.0)	10 (20.0)	2 (4.0)
Neutropenia	2 (4.0)	4 (8.0)	12 (24.0)	8 (16.0)
Thrombocytopenias	5 (10.0)	1 (2.0)	4 (8.0)	1 (2.0)
Total	11 (22.0)	08 (16.0)	30 (60.0)	12 (24.0)
Non-Hematologic				
Mucositis	1 (2.0)	2 (4.0)	1 (2.0)	0 (0)
Constipation	2 (4.0)	3 (6.0)	0 (0)	0 (0)
Anorexia	2 (4.0)	2 (4.0)	0 (0)	0 (0)
Vomiting	1 (2.0)	0 (0.0)	2 (4.0)	0 (0)
Alopecia	0 (0)	2 (4.0)	0 (0)	0 (0)
Ototoxicity	0 (0)	1 (2.0)	0 (0)	0 (0)
Peripheral Neuropathy	0 (0)	1 (0)	0 (0)	0 (0)
Rash	0 (0)	0 (0)	1 (2.0)	0 (0)
Diarrhoea	0 (0)	0 (0)	1 (2.0)	1 (2.0)
Total	06 (12.0)	11 (22.0)	05 (10.0)	01 (2.0)

Table 5: *Distribution according to biochemical derangements.*

Grade	Increased biochemical parameter				
	Bilirubin	Creatinine	Alkaline phosphatase	AST	ALT
Grade 1, n (%)	0 (0)	2 (4.0)	0 (0)	0 (0)	0 (0)
Grade 2, n (%)	1 (2.0)	2 (4.0)	1 (2)	0 (0)	0 (0)
Grade 3, n (%)	0 (0)	0 (0)	0 (0)	1 (2.0)	1 (2.0)
Total	1 (2.0)	4 (8.0)	1 (2.0)	1 (2.0)	1 (2.0)

Abbreviations: AST-Aspartate aminotransferase, ALT -Alanine Aminotransferase.

In the present study, we found that Pemetrexed and cisplatin combination resulted in improved tumour response in advanced NSCLC (adenocarcinoma) patients. After 6 cycles, partial response, complete response, stable disease and progressive disease were found in 24 patients (48%), 6 patients (12%), 11 patients (22%) and 9 patients (18%) respectively. The objective response rate achieved was 60% and clinical benefit rate was 82% after 6 cycles of chemotherapy. Out of 24 patients showing partial response, after 6 cycles, 17 patients (34%) were of stage IV and 7 patients were of stage III B which shows a good response at an advanced stage. Drop in number of partial remission, from 3 cycles to 6 cycles (36 patients after 3 cycles to 24 patients after 6 cycles) can be explained by an increase in the number of patients showing complete remission as well as increase in patients showing progressive disease. This indicates an overall good response after 6 cycles which is more, and comparable with other studies [6,7,10].

In the phase II trial, Manegold et al. [6] evaluated Pemetrexed plus cisplatin as first line treatment in chemotherapy-naive patients with NSCLC. Thirty-six chemotherapy-naive patients with advanced adenocarcinoma or squamous cell NSCLC received 500 mg/m^2 Pemetrexed plus 75 mg/m^2 cisplatin every 21 day. Out of the total, 14 patients (39%) achieved objective partial remission, while 17 patients (47%) had stable disease as their best response. Partial remission response was slightly higher in patients with stage IV disease (57%). Fifty-six percent of patients remained progression free at 6 months and 33% percent remaining progression free one year. The median survival was 10.9 months. The 6-month and 1-year survival probabilities documented were 81% and 50%, respectively [6]. Similarly, Shepherd et al. [7] in a phase II trial evaluated Pemetrexed plus cisplatin as first-line therapy in 31 patients with advanced NSCLC. Out of 29 patients evaluable, 13 patients achieved partial remission for an overall response rate of 45%. The response rate observed in stage IV patients was 45.8%. Median survival rate of the entire group was 8.9 months and the 1 year survival rate was 49% [7].

Scagliotti et al. in phase III, non-inferiority, randomized, comparative trial in 1,725 chemotherapy-naïve stage IIIB or IV NSCLC patients documented pemetrexed and cisplatin combination to be non-inferior in comparison to gemcitabine and cisplatin combination in terms of survival and response rates. Objective response rates were comparable between the two arms (cisplatin and pemetrexed=30.6%; cisplatin and gemcitabine=28.2%). Subgroup analysis of the study demonstrated that cisplatin and pemetrexed in patients with adenocarcinoma resulted in significantly better survival than cisplatin and gemcitabine (adenocarcinoma: n=847, 12.6 versus 10.9 months, P=03) [10]. These results suggest that pemetrexed is highly effective for the treatment of nonsquamous NSCLC [10].

Studies have confirmed the predictive effect of histology for pemetrexed and the survival advantage for pemetrexed in patients with nonsquamous NSCLC [17]. These observations are further supported by two meta-analyses of randomized clinical trials [18].

One potential explanation for pemetrexed sensitivity in NSCLC histologic types may relate to thymidylate synthase expression levels. Overexpression of thymidylate synthase expression could be responsible for reduced sensitivity to pemetrexed. Thymidylate synthase and S phase kinase–associated protein (Skp2) are commonly up-regulated in NSCLC patients with squamous cell than in patients with adenocarcinoma. These differences in expression levels may correlate with high pemetrexed sensitivity in adenocarcinoma. [10,16,19-22].

Over all, the combination of pemetrexed with cisplatin in our study was well tolerated, with few grade 3 and 4 hematologic and non-hematologic toxicities. The most prevalent hematologic toxicities were leukopenia and granulocytopenia.

In non-hematologic, gastrointestinal-related toxicities were commonly prevalent. The toxicity profile observed in this study was similar to earlier reported studies [6-10] and support the favorable safety profile of pemetrexed with cisplatin.

In summary, the combination of pemetrexed with cisplatin was active, efficacious and well tolerated as first line therapy in advanced NSCLC adenocarcinoma patients. Although robust multicentre, randomized control trials are needed to validate these results.

Limitations: Our study can be placed as a pilot study being carried at a single hospital setting in India in selected populations. The study assessed short-term treatment outcomes. Further randomized trials/studies are warranted to recommend this combination regimen as first-line therapy.

Conclusion

Pemetrexed and Cisplatin combination was found to be active and efficacious as first line chemotherapy in advanced NSCLC adenocarcinoma patients. The combination was well tolerated with minimal grade 3/4 toxicity.

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Citation: *Jain K, Bapna A, Somani N, et al.. Efficacy and safety of pemetrexed and cisplatin chemotherapy as first line in advanced stage of lung adenocarcinoma. J Mol Oncol Res. 2018;2(3):1-6.*

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