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Research Article

Evaluation of Response and Toxicity of Pemetrexed-Carboplatin Versus Paclitaxel-Carboplatin as First-Line Treatment in Metastatic NSCLC

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Abstract

Non-small cell lung cancer (NSCLC) accounts for 80-85% of all lung cancer approximately. The paclitaxel-carboplatin combination is the established standard regimen of choice in metastatic NSCLC. Pemetrexed, a folate antimetabolite is also effective against non-small cell lung cancer. To compare the response and toxicity of the Pemetrexed-Carboplatin regimen with Paclitaxel-Carboplatin in the treatment of metastatic NSCLC. This Quasi-experimental study was conducted from three centers of Dhaka city. 80 patients (40 patients on each arm) who met the inclusion criteria of the study were enrolled. Arm-A received 500mg/m^2 Pemetrexed (Day 1) plus Carboplatin; AUC=5 (Day 1) IV, in another arm, 175mg/m^2 Paclitaxel (Day 1) plus Carboplatin AUC=6; (Day 1) IV, dexamethasone was given 12 mg on night before and on the morning of chemotherapy of each cycle & repeated every 21 days for 6 cycles; were given. Both outcome and toxicities were evaluated. Regarding the tumor control, there was no statistically significant difference in both arms at the follow-up after 6 weeks of completion of chemotherapy [Partial response was seen in 24 (60.00%) patients in Arm-A and in 22 (55.00%) patients in Arm-B, p= 0.58]. Grade ≥3 neutropenia was seen in 09 (22.50%) patients of the Arm-A and 20 (50.00%) patients of Arm-B, p<0.005. Treatment-emergent alopecia was significantly higher in Arm-B [Arm-A, 07 (17.50%) vs Arm-B, 22 (55.00%) p<0.05]. Other non-hematological toxicity was also assessed in both arms and there was no significant difference in the frequency of adverse events. This study supports the fact that Pemetrexed-Carboplatin-based chemotherapy may be equally effective with less haematologic & non-haematologic toxicity than the Paclitaxel-Carboplatin-based chemotherapy regimen.

Keywords

Response, Toxicity, Paclitaxel, Carboplatin, NSCLC

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1. Introduction

Cancer is a group of diseases involving abnormal cell growth, which tends to proliferate uncontrolled and potentially invade surrounding structures or spread to other body parts. Due to lifestyle factors and aging of the population cancer is now an emerging health problem. According to GLOBOCON 2020, almost 19.3 million new cancer cases and 10 million deaths occurred in 2020 [1]. Lung cancer is one of the most frequently diagnosed cancers and is the leading cause of death worldwide [2]. More than 95% of cases are associated with smoking. Other risk factors included genetic predisposition, and occupational or environmental exposure to carcinogens, like arsenic, asbestos, beryllium, cadmium, chromium, nickel, radon, and vinyl chloride; asbestos is the most common [3]. In Bangladesh, the prevalence of SCLC is 10.20% and NSCLC is 84.80% according to the National Cancer Registry Report of NICRH (2015-2017).

Most of the patients are asymptomatic on presentation—the symptoms are related to the location of tumors. Central tumors produce cough, pain, and hemoptysis, obstructive infective symptoms or lobar collapse may cause dyspnoea [4]. If mediastinum is directly involved or involves mediastinal glands, it presents hoarseness of voice, dysphagia, superior vanacaval obstruction, and pericardial effusion or irritation. Peripheral tumors may grow to a large size before causing symptoms. Patients may present with Pancoast syndrome, features of paraneoplastic syndrome & metastasis [5].

The diagnostic evaluation includes a biopsy or cytology of the primary or the metastatic site in a patient with suspected NSCLC which can be done by image guidance or by bronchoscopy. The staging workup includes history, physical examination, chest X-ray, complete blood counts, liver and renal function tests, serum electrolytes, calcium, and chest & abdominal computed tomography (CT)scans. Additional tests may include bone scintigraphy, CT scan, or magnetic resonance imaging (MRI) of the brain, and pleural fluid aspiration for malignant cytology is recommended for selected cases.

Non-small cell lung cancer (NSCLC) is usually diagnosed at an advanced stage and the majority of the patients are diagnosed either in stage III (Locally advanced) or stage IV (metastatic) [6]. The prevalence of stage-IV NSCLC at presentation is around 47.30% [7]. In stage IV, chemotherapy improves survival in patients with metastatic NSCLC (about 10% 1-year survival rate in untreated patients versus 30% to 35% 1-year survival rate with treatment) [8].

However, subset analysis for histology revealed significant differences. Adding a third chemotherapeutic agent to platinum-based doublets has failed to show a superior survival benefit; response rates improved only at the cost of substantially increased toxicity. Again, chemotherapy is recommended for NSCLC with stage IV or negative test results for ALK rearrangement or sensitizing EGFR mutation or PDL-1 expression is absent or unknown. Combining many of these drugs produces 1-year survival rates of 30-40% and is more efficacious than a single agent [9].

A meta-analysis of large randomized trials indicated that there is a small but significant survival advantage with platinum-based therapy compared with best supportive care. Whereas best supportive care resulted in median survival rates of 4 to 5 months and 1-year survival rates of 5% to 10%, current third-generation regimens of platinum combined with paclitaxel and docetaxel, Paclitaxel, vinorelbine, and pemetrexed have yielded median survivals of 8 to 9 months and 1-year survivals of 35% to 40%.

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Based on the rationale that Asian people might share a substantial degree of pharmacogenetic profiles compared to the Western population, this study hypothesized that Pemetrexed-Carboplatin was comparable in treating Bangladeshi metastatic non-squamous NSCLC patients than the Paclitaxel-Carboplatin regimen. Therefore, this study had the potential to pave the way for a new treatment approach for non-squamous NSCLC patients. Furthermore, this type of comparative analysis may not be conducted in Bangladesh. The study will aim to compare the clinical response and toxicity of the Pemetrexed-Carboplatin regimen with the Paclitaxel-Carboplatin regimen in treating metastatic non-squamous non-small cell lung cancer.

2. Methods

This Quasi-Experimental study was conducted from October 2022 to September 2023. It was a multi-centered study conducted in the Department of Clinical Oncology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Shahbagh, National Institute of Cancer Research & Hospital (NICRH), Mohakhali, and Delta Hospital Limited, Mirpur, Dhaka. A purposive sampling technique was applied. A total of 80 patients were selected according to inclusion and exclusion criteria. The patients of Arm A were treated with 4 cycles of the Pemetrexed plus Carboplatin-based regimen, whereas the patients of Arm B were treated with Paclitaxel plus Carboplatin-based regimen.

Findings of observation were recorded in a semi-structured data collection form. Data were edited and analyzed according to the objectives and variables of the study by using the SPSS software program for Windows, version 23.

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Differences between the two means were assessed by student's t-test. All outcomes were compared by chi-square test in the case of qualitative variables. Fisher's exact test was done when >20% of cells in the cross table had an expected frequency of <5. A p-value of <0.05 in the tailed test was considered statistically significant.

2.1. Inclusion Criteria

1) Clinically diagnosed and histopathologically proven non-squamous non-small cell carcinoma of the lung.
2) Histopathologically or cytopathologically proven metastatic disease (stage IV diseases).

2.2. Exclusion Criteria

1) Those who were not willing.
2) Age <18 & >73 years.
3) Patients with a history of prior chemotherapy or radiotherapy.
4) Eastern Cooperative Oncology Group (ECOG) performance status more than 2.
5) Initial surgery (excluding diagnostic biopsy) of the primary site.
6) Patients with double primaries.
7) Pregnant or lactating woman.
8) Very serious co-morbidity.

3. Result

Table 1. *Baseline characteristics of the study population (n=80).*

Variables	Arm-A (n=40)	Arm-B (n=40)	T-test	*p*-value
Age (years)	58.88 ±6.56	59.75 ±6.73	-.589	.558
Weight (kg)	59.90 ±8.42	58.88 ±6.97	.593	.555
Height (cm)	163.60 ±7.52	162.35 ±8.36	.703	.484

Table 1 resembles the baseline characteristic of the study population. It is evident that, there was homogeneous distribution of the study sample and that none of the baseline characteristics were significant.

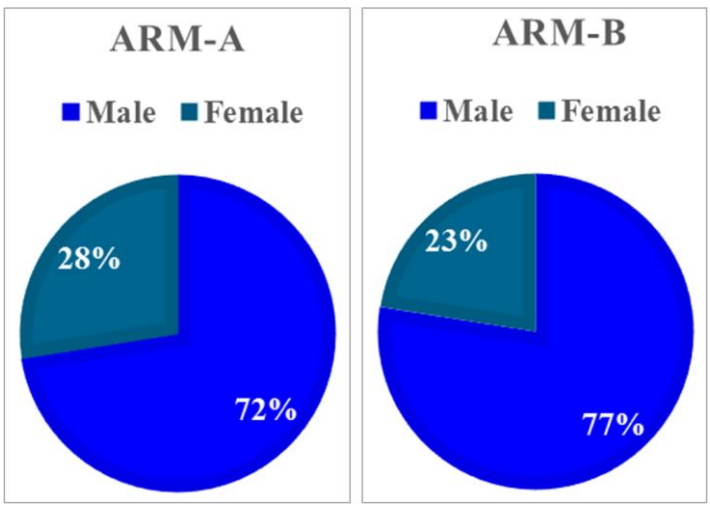

Figure 1. *Distribution of patients according to gender in Arm A and Arm B (n=80).*

Figure 1 shows the distribution of the patients according to gender in both arm A and arm B. Above Pie chart shows the distribution of the patients by gender in both Arms. 80 patients were included in Arm A and Arm B. They were divided into male and female groups, out of which in Arm A, 29 (72%) were male and 11 (28%) were female, and in Arm B, 31 were male (77%), and 9 (23%) were female. (p= 0.61).

Table 2. *Distribution of patients according to the risk factors (n=80).*

Risk factors		Arm-A (n = 40)	%	Arm-B (n = 40)	%	Total (n = 80)	%	*p*– value
Tobacco Related	Smoking	29	72.50	27	67.50	56	70.00	0.62
	Jarda	21	52.50	23	57.50	44	55.00	0.65
Lung disease	COPD	09	22.50	10	25.00	19	23.80	0.79
	Tuberculosis	07	17.50	05	12.50	12	15.00	0.53
Co-Morbidities	HTN & DM	19	47.50	17	42.50	36	45.00	0.65
Occupation	Factory Worker	07	17.50	09	22.50	16	20.00	0.44
	Firewood user	14	35.00	11	27.50	25	31.25	

Table 2 illustrates the distribution of patients according to the risk factors. According to the table, 29 (72.5%) patients in Arm A and 27 (67.5%) patients in Arm B were smokers. A good number of patients were also associated with various lung diseases such as COPD, Asthma, TB etc in both arms.

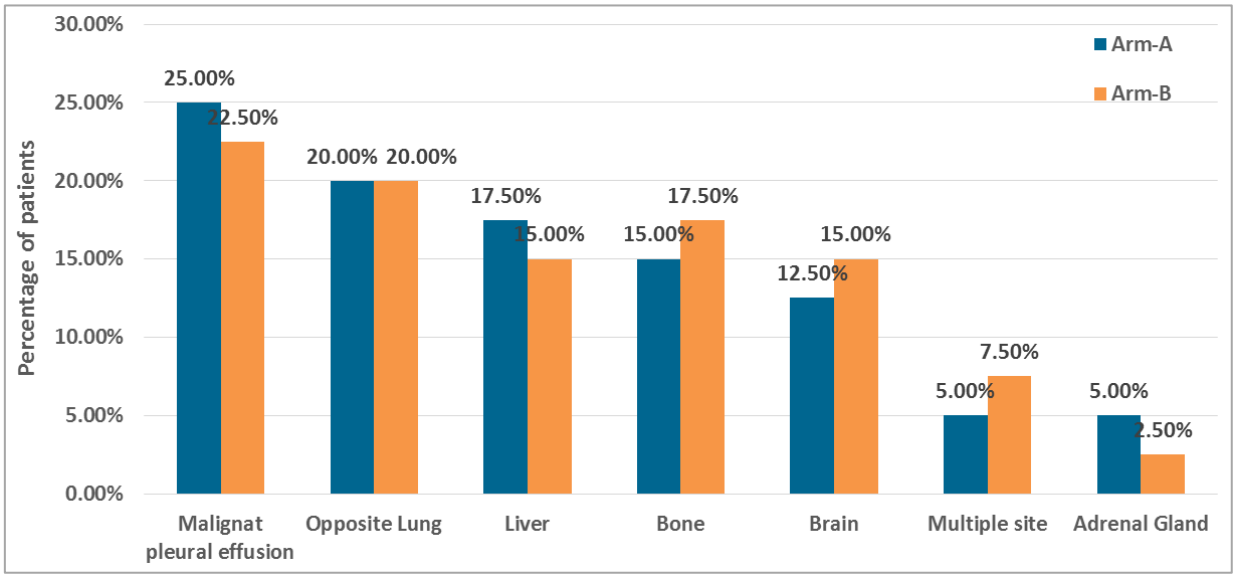

Figure 2. *Distribution of patients according to site of metastasis.*

Figure 2 shows the distribution of patients according to the site of metastasis. The above figure demonstrated that the most commonly observed site of metastasis in both arms was metastatic pleural effusion followed by opposite lung, bone, liver, multiple site, and adrenal gland accordingly. *p*-value=0.99 (insignificant) displayed that the distribution of patients according to the site of metastasis was homogenous.

Table 3. *Response evaluation after 2nd & 3rd Cycle & 6 weeks after completion of chemotherapy (n=80).*

Response (2nd & 3rd cycle)	Arm-A (n=40)	%	Arm-B (n=40)	%	Total (n=80)	%	Chi-square Value	p – value
Complete response (CR)	-	-	-	-	-	-	0.202	0.65

Response (2nd & 3rd cycle)	Arm-A (n=40)	%	Arm-B (n=40)	%	Total (n=80)	%	Chi-square Value	p – value
Partial response (PR)	23	57.50	21	52.50	44	55.00		
Stable disease (SD)	17	42.50	19	47.50	36	45.00		

Response (6th week)	Arm A (n=4)	%	Arm B (n=4)	%	Total (n=80)	%	Chi-Square Value	*p*-value
Complete response (CR)	-	-	-	-	-	-		
Partial response (PR)	24	60.00	22	55.00	46	57.50		
Stable disease (SD)	15	37.50	15	37.50	30	37.50	1.08	0.58
Progressive disease (PD)	01	02.50	03	07.50	04	05.00		

Table 3 shows response evaluation after the 2nd, and 3rd cycles & 6 weeks after completion of chemotherapy. above table showed that, at mid-term evaluation after the completion of 2nd & 3rd cycle chemotherapy, no patients had a complete response, 23 (57.50%) patients had a partial response and 17 (42.50%) had stable disease in Arm A. Whereas in Arm B, no patients had complete response, 21 (52.50%) and 19 (47.50%) patients had partial response & stable disease respectively. On the other hand, there was no complete response in both arm. Partial response was 24 (60%) in Arm A and 22 (55%) in Arm B. 15 (37.50%) patients presented with stable disease in Arm A whereas 15 (37.50%) in Arm B. Progressive disease was reported in 01 (02.50%) in Arm A and 03 (7.50%) in Arm B.

Table 4. *Overall acute hematological toxicities in both arms (n=80).*

Hematological toxicities	Arm A n=40	%	Arm B n=40	%	Total n=80	%	Chi-Square Value	*p* – value
Anemia								
Grade 0	04	10.00	03	7.50	07	8.75		
Grade 1	25	62.50	23	57.50	48	60.00	0.648	0.95
Grade 2	08	20.00	10	25.00	18	22.50		
Grade 3	02	5.00	03	7.50	05	6.25		
Grade 4	01	2.50	01	2.50	02	2.25		
Leucopenia								
Grade 0	06	15.00	02	5.00	08	10.00		
Grade 1	16	40.00	07	17.50	23	28.75		
Grade 2	09	22.50	10	25.00	19	23.75	10.48	0.033
Grade 3	07	17.50	15	37.50	22	27.50		
Grade 4	02	5.00	06	15.00	08	10.00		

Table 4 shows overall acute hematological toxicities in both arms. It can be seen that none of the patients were spared from

anemia. The severity of anemia was slightly higher in Arm B compared to Arm A 11 (27.5%) patients developed Grade 2 or more anemia in Arm-A, whereas 14 (35%) patients in Arm-B. This finding was statistically insignificant between the two arms (p >0.05).

Leucopenia of various grades was predominant in both the Arms. It was seen that Grade 3 or more leucopenia was seen in 09 patients (22.50%) vs 21 patients (52.50%) among Arm A and B respectively. The finding was statistically significant (p <0.05).

Neutropenia, like leucopenia of various grades was predominant in both the Arms. It was seen that Grade 3 or more neutropenia was seen in 09 patients (22.50%) vs 20 patients (50%) among Arm A and B respectively. The finding was statistically significant (p <0.05).

Grade 2 and Grade 3 thrombocytopenia was seen more in Arm B compared to Arm A. 13 (32.50%) patients in Arm A and 16 (40%) in Arm B developed Grade 2 and 3 thrombocytopenia. The finding was statistically insignificant (p >0.05).

Grade 3 febrile neutropenia was seen to be more in Arm B than Arm A. 05 (12.50%) patients in Arm A, whereas 08 (20.00%) in Arm B developed grade 3 febrile neutropenia respectively. The finding was statistically insignificant (p >0.05).

Table 5. *Overall acute non-hematological (alimentary) toxicities observed during Chemotherapy (n=80).*

Toxicities	Arm A		Arm B		Total		Chi-square value	*p* – value
	n=40	%	n=40	%	n=80	%		
Nausea								
Grade 0	04	10.00	08	20.00	12	15.00		
Grade 1	23	57.50	21	52.50	44	55.00	1.6	0.65
Grade 2	12	30.00	10	25.00	22	27.50		
Grade 3	01	2.50	01	2.50	02	22.50		
Vomiting								
Grade 0	26	65.00	25	62.50	51	63.75		
Grade 1	11	27.50	12	30.00	23	28.75	0.06	0.96
Grade 2	03	7.50	03	7.50	06	7.50		
Diarhoea								
Grade 0	26	65.00	25	62.50	51	63.75		
Grade 1	11	27.50	13	32.50	24	30.00	0.52	0.91
Grade 2	02	5.00	01	2.50	03	3.75		
Grade 3	01	2.50	01	2.50	02	2.50		
Mucositis								
Grade 0	25	62.50	26	65.00	51	63.75		
Grade 1	11	27.50	10	25.00	21	26.25	1.2	0.75
Grade 2	03	7.50	04	10.00	07	8.75		
Grade 3	01	2.50	00	00	01	1.25		

Table 5 illustrates overall acute non-hematological (alimentary) toxicities observed during chemotherapy. Incidence of nausea was almost similar on both arms. 12 (30.00%) and 01 (02.50%) patients in Arm A, whereas 10 (25%) and 01 (2.50%) patients in Arm B developed grade 2 and grade 3 nausea.

The incidence of vomiting and diarrhea were also similar in both arms. Grade 2/3 mucositis was similar in Arm A and Arm B, 04 (10.00%) and 04 (10.00%).

4. Discussion

Patients from various medical centers across Dhaka who met the study's specific criteria were included in this research endeavor. In this study, the average age of patients at the time of diagnosis was 59.32 ±6.70. Tao Chen et al. (2019) revealed the average age of patients at diagnosis of NSCLC was 68 years [11]. Interestingly, the result of this study closely mirrors the data from the Cancer registry report (2015-2017) of NICRH, Dhaka, which reported the average age of patients at diagnosis was 58.85 ±12.14. This alignment between this study's findings and the registry's data adds further depth to our understanding of the patient demographics in this context.

Out of the 80 patients under scrutiny, a substantial majority, comprising 60 (75%) individuals were male, while the remaining 20 (25%) patients were female. The overarching gender ratio, therefore, stands at an appreciable 3:1, firmly indicating a pronounced male predominance within this patient cohort. Notably, this observation echoes the findings of Ruquiya Afrose et al. (2015) in their study, which discerned a higher incidence among males as compared to females, with a distribution of 81% and 19% respectively. Cancer Registry Report (2015-2017) of NICRH observed a higher incidence of Lung cancer among males 84.50% than females 14.50% [12].

The analysis encompassed an assessment of multiple risk factors, with smoking emerging as the foremost global contributor to lung cancer. Culminating in a total of 56 patients (70%) among the entire study population who had a history of smoking. It is noteworthy that smoking has been unequivocally established as the most significant risk factor for non-small cell lung cancer, as delineated by the American Cancer Society in 2019 [13].

The partial response rate for large cell carcinoma was 0% in Arm A and 66.70% in Arm B. In Arm A, 50.00% of patients exhibited stable disease, while in Arm B, this percentage was 33.30%. Progressive disease was observed in 50.00% of patients in Arm A and 0% in Arm B. Jules et al. (2017) observed in their research that Paclitaxel based chemotherapy showed superior overall survival than Pemetrexed based chemotherapy [14].

In the assessment of hematological toxicities, the study found that various acute hematological toxicities were commonly observed, including anemia, leucopenia, neutropenia, and thrombocytopenia. In particular, when comparing Arm-B to Arm-A, there were statistically significant differences in the incidence of grade 3/4 leucopenia (52.50% in Arm-B compared to 22.50% in Arm-A, p= <0.05) and neutropenia (50% in Arm-B compared to 22.50% in Arm-A, p= <0.05). These findings align with previous research conducted by Jose Rodrigues-Pereira et al. (2011) providing further support for the observed differences in hematological toxicity between the two treatment arms [15].

5. Conclusion

According to this study, it may be concluded that the Pemetrexed plus Carboplatin-based chemotherapy regimen was equally effective with less haematologic as well as non-haematologic toxicity in comparison to Paclitaxel plus Carboplatin-based chemotherapy regimen.

Abbreviation

ALK	Anaplastic Lymphoma Kinase
COPD	Chronic Obstructive Pulmonary Disease
NSCLC	Non-Squamous Non-Small Cell Lung Cancer
NICRH	National Institution of Cancer Research and Hospital
PD-L1	Programmed Death-Ligand 1
SCLC	Small Cell Lung Cancer
TB	Tuberculosis

Conflicts of Interest

The authors declare no conflicts of interest.

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