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Review Article

Evaluation of Response and Toxicities of Irinotecan-Cisplatin Versus Etoposide-Cisplatin in Extensive Stage Small Cell Lung Cancer

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Abstract

Background: Small cell lung cancer accounts for 15% of all lung cancer approximately. Etoposide-Cisplatin combination is the established standard regimen of choice. Irinotecan, a topoisomerase inhibitor is effective against small cell lung cancer. Several studies showed the superiority of Irinotecan-Cisplatin regimen combination over Etoposide-Cisplatin regimen.

Aims and Objectives: To compare the response and toxicities of Etoposide-Cisplatin regimen with Irinotecan-Cisplatin in the treatment of Extensive Stage Small cell lung cancer.

Material and Method: Quasi-experimental study was conducted from May 2019 to April 2020 in various center of Bangladesh. 64 patients (32 patients on each Arm) who met the inclusion criteria of the study were enrolled. Arm A received Irinotecan 60mg/m2 on day 1, 8,15 plus Cisplatin 60 mg/m2 on day 1 every 4 weeks for 6 cycles. In another arm, Etoposide (80mg/m2 IV on day 1-3) plus Cisplatin (80 mg/m2 IV on day 1) every 3 weekly for 6 cycles was given. Each patient was evaluated before, during and after the completion of the treatment. The follow up was done at 6 and 12 weeks after the completion of the treatment.

Result: The overall mean age was 56.84 ± 9.01 within the age range of 34-70 years. Overall, cough 54 (84.38%) followed by dyspnea 28(77.78%) was the most common presentation. Both outcome and toxicities were evaluated. Regarding the tumor control there was no statistically significant difference in both arms at 6 weeks (p = 0.76) and 12 weeks (p = 0.74) of follow-up. Grade ≥2 anaemia was common in Arm B than Arm A 22 (68.75%) vs 16 (50%)), p = 0.28. Grade 3 neutropenia was seen in 04 (12.5%) patients of the Arm A and 08 (25%) patients of Arm B, p = 0.26. The highest grade of nausea and vomiting (grade 3) was seen in 05 (15.6%) patients of Arm A and 03 (9.4%) patients of Arm B, p = 0.46. Significant grade ≥1 diarrhoea was 30 (93.7%) in Arm A and 6 (18.8%) in Arm B, p = <0.001. 09 (28.125%) patients from Arm A and 15 (46.9%) patients from Arm B developed febrile neutropenia, p = 0.21. Grade ≥1 Alopecia 28 (84.4%) in Arm b and 04 (12.5%) in Arm, p = <0.001.

Conclusion: This study supports the fact that Irinotecan-Cisplatin based chemotherapy schedule is not inferior and almost equally effective to Etoposide-Cisplatin based chemotherapy regimen.

Keywords: Lung Cancer; Etoposide-Cisplatin; Irinotecan-Cisplatin Regimen

Introduction

Cancer is a leading health problem all over the world. It affects multiple sites of human body. Lung cancer was not identified as a disease until mid-1700. In 1761 lung cancer identified as a distinct disease. Lung cancer is the leading cause of cancer related morbidity & mortality. According to GLOBOCAN 2020, global cancer incidence was 1,92,92,789 in 2020 and cancer-related death was 99,58,133 [1]. As per GLOBOCAN 2020, lung cancer is the top most frequent cancer with an incidence of 22,06,771 (11.4%) and mortality of 17,96,144 (18%). Lung cancer is the 4th most prevalent cancer in both men and women in Bangladesh, with an incidence of 12,999 (8.3%) and the 2nd most common cause of cancer-related mortality, accounting for 12,003 (11%) cancer deaths. According to the World Health Organization, lung cancer would be the most frequent cancer in both men and women by 2040, with an estimated incidence of 26,738 cases/year. Regrettably, there are currently no national statistics available in Bangladesh on the frequency and incidence of cancer in the general population. However, there have been some hospital-based statistics collected by the National Institute of Cancer Research and Hospital (NICR&H), Dhaka. According to this Hospital Based Cancer Registry report (2015- 2017) by the NICR&H, published in December 2020, lung was the leading site of cancers (5887,16.6%). Lung cancer, also known as bronchogenic carcinoma, is a type of cancer that starts in the airways or pulmonary parenchyma. SCLC accounts 15% of lung cancers [2]. Several environmental and lifestyle factors have been linked to the development of lung cancer, with cigarette smoking being the most common cause, accounting for over 90% of all lung cancer cases. Radiation therapy (RT), secondhand smoke exposure, occupational lung carcinogens (such as asbestos, radon, arsenic, chromium, and nickel), polycyclic aromatic hydrocarbons, ionizing radiation exposure, indoor and outdoor air pollution, and pulmonary fibrosis are all known risk factors for lung cancer [3]. SCLC characterized by a rapid tumor growth and an early haematogenous spread. Presenting symptoms are cough, haemoptysis, dyspnea, chest pain, hoarseness of voice, pleural involvement, superior venacava obstruction syndrome, pancoast syndrome, features of paraneoplastic syndrome & metastasis. The diagnostic evaluation includes a biopsy or cytology of the primary or the metastatic site in a patient with suspected SCLC which can be done by image guidance or by bronchoscopy. The staging workup includes detailed history, physical examination, chest X-ray, complete blood counts, liver and renal function tests, serum electrolytes, calcium, lactate dehydrogenase, chest & abdominal computed tomography (CT) scans. Additional tests may include bone scintigraphy, CT scan or magnetic resonance imaging (MRI) of the brain, pleural aspiration for malignant cytology is recommended for selected cases. Two stage staging system for SCLC was introduced by Veterans Administration Lung Study Group (VASG) Limited & Extensive. Disease fitting into a single radiation port, typically confined to one hemithorax & regional nodes are termed as limited stage. Any disease that does not meeting the criteria of limited stage is extensive stage. Approximately two-thirds of patients with SCLC have extensive disease [4]. As per AJCC version 8, in applying the TNM classifications to the VALSG, limited-stage SCLC is defined as stage I-III (T any, N any, M0) that can be safely treated with definitive radiation therapy (RT), excluding T3-4 due to multiple lung nodules that are too extensive or have tumor / nodal volume that is too large to be encompassed in a tolerable radiation plan. Extensive-stage SCLC (ES SCLC) is defined as stage IV (T any, N any, M1a/b/c) or T3-4 due to multiple lung nodules as previously described. The prognostic factors for patients with SCLC are tumor-related factors such as stage of the disease, LDH, alkaline phosphatase, WBC, platelet count, molecular/biologic markers, patient-related factors such as weight loss, comorbidity, performance status, continued use of tobacco and environment-related factors such as chemotherapy, thoracic radiotherapy, and prophylactic cranial radiotherapy [5]. SCLC has a greater growth fraction, a faster doubling time, and more widespread metastases than other cancers [6]. It is a very aggressive cancer. The natural history of untreated SCLC is dismal with median survival of 12 weeks for untreated patients with limited-stage SCLC and 6 weeks for untreated patients with extensive-stage SCLC. Patients with limited-stage SCLC have a 5-year survival rate of 15 to 25%, while patients with extensive stage SCLC have a 5-year survival rate fewer than 1% [6]. SCLC is a highly responsive to chemotherapy. In 1970, the most commonly used regimen for SCLC incorporated Cyclophosphamide, Doxorubicin & Vincristine. In late 1980s Etoposide-Cisplatin (EP) regimen was introduced. Based on randomized controlled studies, EP was established as superior frontline therapy for ES SCLC in early 1990s. Over the past three decades, the standard regimen for ES SCLC is Etoposide– Cisplatin (EP) [7]. Irinotecan hydrochloride, a topoisomerase I inhibitor is effective against small cell lung cancer. Preliminary studies with irinotecan revealed the promising outcome against SCLC and subsequent Phase II study with Irinotecan & Cisplatin (IP) reported a complete response rate of 29% and an overall rate of 86% in patients with ES SCLC [8]. The Median survival time & overall survival for IP arms & EP arms were 12.8 versus 9.4 months and 84.4% versus 67.5% respectively (p = 0.002). The severe toxicity in the IP arm was grade 3/ 4 diarrhea whereas the severe myelosuppression was observed more frequently in EP arm. Despite the positive role of IP for ES SCLC two subsequent large-scale phase III trials failed to confirm the superiority of IP over EP in the United states, Australia & Canada [9]. The cause of inconsistent result for IP regimen between Japanese & Western populations has not been elucidated yet. It is possible that the difference in efficacy and toxicity in the randomized trials may partly be because the polymorphisms of genes involved in the metabolism or transport of chemotherapy vary among ethnic populations [10]. Due to rapid emergence of clinical drug resistance inevitably results in the death of more

than 90% of affected patients [11]. Due to emergence of resistant clones it is necessary to innovate newer agents to treat extensive stage SCLC. Irinotecan hydrochloride can be a good alternative to Etoposide.

Materials and Methodology

This was a Quasi-Experimental Study. The patients were selected by convenient and purposive sampling method. A total of 64 patients were included in this study, 32 patients were allocated in Arm A and the rest 32 in Arm B. The study was conducted in the Department of Clinical Oncology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Shahbagh, Dhaka, Bangladesh, and National Institute of Cancer Research and Hospital, Mohakhali, Dhaka, Bangladesh. At May, 2019 to April, 2020 (One year). Histologically proven newly diagnosed extensive stage small cell carcinoma of lung with informed consent were enrolled for the study. Each arm received treatment as mentioned below. Arm -A: Treated with in fusional Irinotecan-Cisplatin regimen. Arm - B: Treated with in fusional Etoposide- Cisplatin regimen. All patients had a baseline complete blood count, biochemical evaluation, creatinine clearance rate (CCR), cardiac evaluation, inclusive of an ECG and 2D ECHO before the start of treatment. CT scan 6 weeks post treatment was done as and when required. Patients were assessed for acute toxicities during the treatment by weekly investigations and clinical examination by using National Cancer Institute Common Terminology Criteria for Adverse Events (NTC-CTCAE) v 5.0 criteria. Treatment response evaluation was done using RECIST criteria during chemotherapy as a mid-cycle evaluation and then at 6, 12 and 18 weeks of completion of chemotherapy. During follow up, few patients having complete response or good response to chemotherapy especially with residual thoracic disease and low bulk extrathoracic metastatic disease and indicated for radiotherapy, then consolidative thoracic radiotherapy was offered. Those patients who developed progressive disease and suitable for further treatment second line chemotherapy and palliative radiotherapy was offered.

Inclusion criteria

- Clinically diagnosed and histopathologically proven small cell carcinoma of lung
- Extensive stage small cell lung cancer (AJCC 8 TNM Staging)

Exclusion criteria

- Age below 18 years and above 70 years
- Patients with history of prior chemotherapy or radiotherapy
- Initial surgery (excluding diagnostic biopsy) of the primary site
- Patients with brain metastasis and SVCO requiring radiotherapy
- Eastern Cooperative Oncology Group (ECOG) performance status>2
- Patients with double primaries
- Pregnant or lactating woman

Analysis and Interpretation of data

The information's that were found, interpreted, conclusion and recommendation were drawn in order to address the objectives of the study. The possibility of bias in the study was acknowledged and limited as possible. The data was tabulated in separate table for both Arm A and B. Those were checked, edited, coded manually and finally saved in the computer. Data analysis was done according to the objectives of the study by using the SPSS software program for Windows, version 25.0. Differences between two means were assessed by T-test. All outcomes were compared by chi square test. A p value of ≤0.05 in two tailed test was considered as statistically significant.

Ethical considerations

In this study the following criteria were set to ensure maintaining the ethical values:

- All patients were given an explanation of the study including the risks and benefits.
- All patients were included in the study after taking their informed written consent.
- Explanation regarding participant's right to refuse or accept to participate in the study.
- For safeguarding confidentiality and protecting anonymity of the patient was given a special code number which was used in every step of the study.
- All data obtained during the study period from the patient remained confidential.

Results

Among 64 patients, 32 patients were allocated in Arm A and the rest 32 in Arm B. The patients of Arm A were treated with 6 cycles of the Irinotecan-Cisplatin based regimen, whereas the patients of Arm B were treated with Etoposide-Cisplatin based regimen. All patients were admitted to the hospital for the administration of chemotherapy in both Arms. Both the Arms were given Inj. Filgrastim on 24 hours of completion of the chemotherapy. The patients were evaluated during the treatment and after the completion of chemotherapy according to the follow-up schedule. For a patient, when any toxicity developed in multiple cycles of treatment, the highest grade was taken for statistical analysis. The statistical data were analyzed by Chi-square test, Fisher's exact test and Independent T-test where applicable. The p-value less than 0.05 was taken as significant. Observations and results of this study are shown in the following tables and graphs.

Table 1: Baseline characteristics of the study population (N = 64).

Variables	Arm A (n = 32)	Arm B (n = 32)	T test	P-value
Age	57.25 ± 9.62	56.44 ± 8.61	0.355	0.72
Weight	52.56 (±10.17)	53.86 (±7.64)	-0.57	0.56
Height (cm)	165.53 ± 3.60	163.81 ± 4.78	1.63	0.12
BSA	1.58 ± 0.13	1.59 ± 0.10	-0.35	0.73

Table 1 showed characteristic of the study population enrolled in this study. This shows that none of the baseline character were significant thus there was homogenous distribution of the study sample.

Table 1 showed above data shows that most of the patients were in the 51-60 age group in both Arms, i.e., 13 (40.7%) and 14 (43.8%) in Arm A and Arm B respectively. No significant difference was observed between the two Arms (p = 0.72).

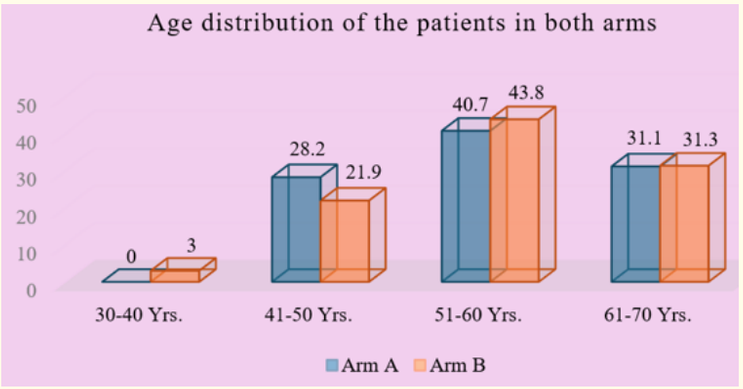

Figure 1: Column chart showed distribution of patients according to age group in both the arms (N = 64).

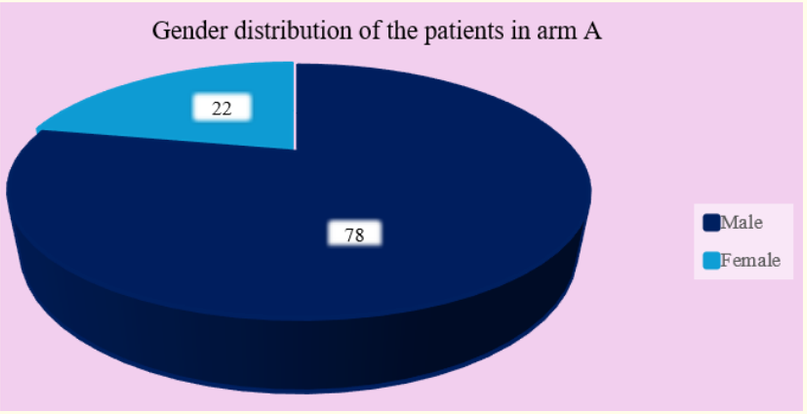

Figure 2: Pie chart showed distribution of patients according to gender in arm A (N = 32).

Figure 2, 3 showed distribution of the patient by gender in both the Arms. 64 patients were included in Arm A and Arm B. They were divided into male and female groups, out of which in Arm A, 25 (78%) were male and 7 (22%) were female, and in Arm B, 22 were male (69%), and 10 (31%) were female. Overall, male and female ratio were 2.8:1 (p = 0.403).

Table 2 showed various risk factors identified among Arm A and Arm B. 25 (78.12%) patients in Arm A and 23(71.88%) 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. The findings were statistically insignificant (p > 0.05).

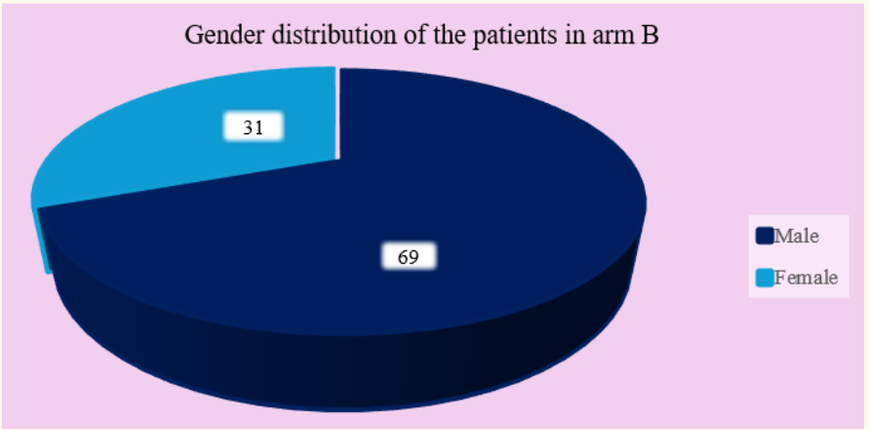

Figure 3: Pie chart showed distribution of patients according to gender in arm B (N = 32).

Table 2: Distribution of patients according to the risk factors (N = 64).

Risk factors		Arm A (n = 32)	Arm B (n = 32)	Overall (N = 64)	Chi-square test	P-value
Tobacco related	Smoking	25(78.12%)	23(71.88%)	48(75%)	0.28	0.87
	Jarda	18(56.25%)	20(62.5%)	38(59.38%)		
	Betel Leaf	27(84.38%)	30(93.75%)	61(89.06%)		
Lung disease	COPD	9(28.12%)	11(34.38%)	20(31.25%)	0.93	0.63
	Asthma	5(15.63%)	6(18.75%)	11(17.19%)		
	Tuberculosis	4(12.50%)	2(6.25%)	6(9.37%)		
Others Comorbidities	Hypertension Diabetes Mellitus	13(40.63%)	16(50%)	29(45.31%)	0.57	0.46
Occupation	Factory Worker	4(12.50%)	8(25%)	12(18.75%)	2.22	0.14
	Firewood user	11(34.38%)	7(20%)	18(21.88%)		

Table 3: Distribution of patients according to the clinical presentations in both the arms (N = 64).

Symptoms	Arm A (n = 32)	Arm B (n = 32)	Overall (N = 64)	Chi-square test	P-value
Cough	28(87.5%)	26(81.25%)	54(84.38%)	0.47	0.49
Dyspnea	12(37.5%)	16(50%)	28(77.78%)	1.01	0.31
Hemoptysis	10(31.25%)	7(21.88%)	17(26.56%)	0.72	0.36
Chest Pain	4(12.5%)	9(28.13%)	13(20.31%)	2.41	0.12
Infection	11(34.38%)	16(50%)	27(42.19%)	1.60	0.21
Hoarseness	4(11.43%)	1(02.86%)	5(07.14%)	1.95	0.16
SVCO	6(12.5%)	8(25%)	14(21.88%)	0.37	0.55
Others (weight loss, loss of appetite, weakness etc.)	10(31.25%)	12(37.5%)	22(34.38%)	0.27	0.60

Table 3 showed most common presentation in both arms were cough followed by dyspnea. The majority of the patients in Arm A presented with cough (28 out of 32, 87.5%) followed by dyspnea (12 out of 32, 37.5%), whereas patients in Arm B presented with cough (26 out of 32, 81.25%) followed by dyspnea (16 out of 32, 50%). The findings were statistically insignificant ($p > 0.05$).

Table 4 showed TNM staging of the patient in both Arms. The finding was statistically insignificant, $p > 0.05$ which indicate homogenous distribution of the study population in both Arms.

Table 4: Distribution of patients according to AJCC 8th edition T, N and M stage (N = 64).

Variable	Arm A (n = 32)	Arm B (n = 32)	Over all (N = 64)	Chi-square test	P-value
T stage					
T2	5(15.62%)	6(18.75%)	11(17.19%)	2.64	0.27
T3	14(43.75%)	19(59.37%)	33(51.56%)		
T4	13(40.63%)	7(21.88%)	20(31.25%)		
N stage					
N1	11(34.37%)	9(28.13%)	20(31.25%)	0.29	0.86
N2	10(31.26%)	11(34.37%)	21(32.81%)		
N3	11(34.37%)	12(37.5)	23(35.94%)		
M stage					
M0	11(34.37%)	10(31.25%)	21(32.81%)	0.31	0.96
M1a	11(34.37%)	12(37.5%)	23(35.94%)		
M1b	4(12.6%)	3(9.38%)	7(10.94%)		
M1c	6(18.75%)	7(21.87%)	13(20.31%)		

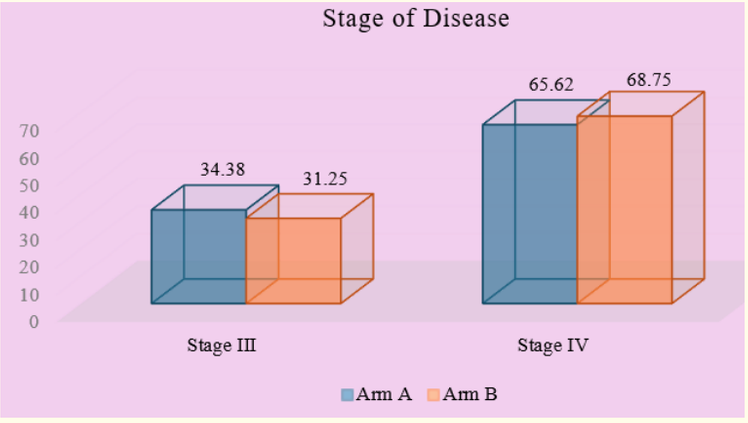

Figure 4: Column chart showed distribution of patients according to the stage group in both the Arms (N = 64).

Figure 4 showed the majority of the patient presented with Stage IV disease in both Arms. In Arm A, 11 (34.38%) and 21 (65.62%) patients were in Stage III and IV, whereas 10 (31.25%) and 22 (68.75%) patients were in Stage III and IV respectively in Arm B. The finding was statistically insignificant ($p > 0.05$) which shows that there was the uniform distribution of the cases.

Table 5: Midterm evaluation after completion of 3 cycles of chemotherapy (N = 64).

Response	Arm A (n = 32)	Arm B (n = 32)	Overall (N = 64)	Chi-square test	P-value
Complete response (CR)	5(15.63%)	6(18.75%)	11(17.19%)	0.45	0.80
Partial response (PR)	20(62.5%)	21(65.63%)	41(64.06%)		
Stable disease (SD)	7(21.87%)	5(15.62%)	12(18.75%)		

Table 5 showed that at mid-term evaluation after the completion of 3 cycle chemotherapy, 05 (15.63%) patients had complete response, 20 (62.5%) patients had partial response and 07 (21.87%) had stable disease in Arm A. Whereas in Arm B, 06 (18.75%) and 21 (65.63%) patients had complete response and partial response respectively whereas 05 (15.62%) had stable disease. The findings were statistically insignificant (p = 0.80).

Table 6: Clinical response observed at the 1st follow-up (6 weeks after completion of chemotherapy) (N = 64)

Response	Arm A (n = 32)	Arm B (n = 32)	Overall (N = 64)	Chi-square test	P-value
Complete response (CR)	15(46.9%)	19(59.4%)	34(53.1%)	1.15	0.77
Partial response (PR)	11(34.4%)	9(28.1%)	20(31.3%)		
Stable disease (SD)	4(12.5%)	3(9.4%)	7(10.9%)		
Progressive disease (PD)	2(6.2%)	1(3.1%)	3(4.7%)		

Table 6 showed the response of primary tumor observed during the first follow-up at an interval of 6 weeks after the completion of the planned treatment. Complete response (CR) was 15(46.9%) and 19 (59.4%) in Arm A and B respectively. Partial response was 11(34.4%) in Arm A and 09(28.1%) in Arm B. 04 (12.5%) patients presented with stable disease in Arm A whereas 03 (9.4%) in Arm B. Progressive disease was reported in 02(12.5%) in Arm A and 01(3.1%) in Arm B. The findings were statistically insignificant (p = 0.77).

Table 7: Clinical response observed at the 1st follow-up as per smoking habit (N = 64).

Response	Arm A (n = 32)		Arm B (n = 32)		Overall (N = 64)		Chi-square test	P-value
	Smoker (n = 25)	Non smoker (n = 7)	Smoker (n = 23)	Non smoker (n = 9)	Smoker (n = 48)	Non smoker (n = 16)		
Complete response CR)	9(36%)	6(85.7%)	11(47.8%)	8(88.9%)	20(41.7%)	14(87.5%)	10.13	0.002
Partial response (PR)	10(40%)	1(14.3%)	8(34.8%)	1(11.1%)	18(37.5%)	2(12.5%)	3.49	0.061
Stable disease (SD)	4(16%)	0(00%)	3(13.0%)	0(00%)	7(14.6%)	0(00%)	-	-
Progressive disease (PD)	2(8%)	0(0%)	1(4.4%)	0(00%)	3(6.2%)	0(00%)	-	-

Table 7 showed the response attained at 6 weeks after chemotherapy among smokers and non-smokers in both Arms. It shows that 14(87.5%) out of 16 patients had complete responses non-smokers group. On the other hand, only 41.7% patient had complete response among smoker patient. The finding was statistically significant (p = 0.002).

Table 8: Clinical response observed at the 2nd follow-up (12 weeks) after completion of chemotherapy.

Response	Arm A (n = 32)	Arm B (n = 32)	Overall (N = 64)	Chi-square test	P-value
Complete response (CR)	11(34.4%)	14(43.7%)	25(39.1%)	0.59	0.74
Partial response	8(25%)	7(21.9%)	15(23.4%)		
Progressive disease	13(40.6%)	11(34.4%)	24(37.5%)		

Table 8 showed at second follow-up, out of 32, 11 (34.4%) patients had complete response, 08 (25%) patients had partial response and 13(40.6%) had progressive disease in Arm A. whereas, in Arm B, 14 (43.7%) and 07 (21.9%) patients had complete response and partial response respectively whereas 11 (34.4%) had progressive disease. These findings were statistically insignificant (p = 0.74).

Table 9: Clinical response observed at the 2nd follow-up as per smoking habit (N = 64).

Response	Arm A (n = 32)		Arm B (n = 32)		Overall (N = 64)		Chi-square test	P-value
	Smoker (n = 25)	Non smoker (n = 7)	Smoker (n = 23)	Non smoker (n = 9)	Smoker (n = 48)	Non smoker (n = 16)		
Complete response (CR)	6(24%)	5(71.4%)	8(34.8%)	6(66.7%)	14(29.2%)	11(68.8%)	7.90	0.02
Partial response (PR)	7(28%)	1(14.3%)	6(26.1%)	1(11.1%)	13(27.1%)	2(12.5%)		
Progressive disease (PD)	12(48%)	1(14.3%)	9(39.1%)	2(22.2%)	21(43.7%)	3(18.7%)		

Table 9 showed response attained at 12 weeks after chemotherapy among smokers and non-smokers in both Arms. It shows that 14 (29.2%) out of 16 patients had complete responses among smokers group. On the other hand, 11(68.8%) patient had complete response among non-smoker patient. Partial response and Progressive disease were 13(27.1%) and 21(43.7%) and in smoker group and 2(12.5%) and 3(18.7%) in non-smoker group respectively. The finding was statistically significant (p = 0.02).

Table 10: Overall acute hematological toxicities in both the arms (N = 64).

Hematological toxicities	Arm A (n = 32)	Arm B (n = 32)	Overall (N = 64)	Chi-square test	P-value
Anemia					
Grade 1	16(50%)	10(31.25%)	26(40.63%)	2.55	0.28
Grade 2	14(43.75%)	18(56.25%)	32(50%)		
Grade 3	2(6.25%)	4(12.5%)	6(9.37%)		
Leucopenia					
Grade 1	12(37.5%)	7(21.88%)	19(29.69%)	2.68	0.26
Grade 2	16(50%)	17(53.12%)	33(51.56%)		
Grade 3	4(12.5%)	8(25%)	12(18.75%)		
Thrombocytopenia					
Grade 0	16(50%)	12(37.5%)	28(43.75%)	2.75	0.43
Grade 1	10(31.25%)	9(28.12%)	19(29.69%)		
Grade 2	5(15.63%)	7(21.88%)	12(18.75%)		
Grade 3	1(3.12%)	4(12.5%)	5(7.81%)		

Table 10 showed compares the various acute hematological toxicities observed between the two arms from the start of the treatment up to 18 weeks following the completion of the treatment. It can be seen that none of the patients were spared from anemia. The severity of anemia was higher in Arm B compared to Arm A. 14 (43.75%) 02 (6.25%) of patients developed Grade 2 and 3 anemia in Arm B, whereas 18 (56.25%) and 04 (12.5%) patients developed Grade 2 and 3 anemia respectively in Arm A. This finding was statistically insignificant between the two arms (p = **0.28).** Leucopenia of various grades was predominant in both the Arms. It was seen that Grade 2 or more leucopenia was seen in 20 patients (62.5%) vs 25 patients (78.12%) among Arm A and B respectively. The finding was statistically insignificant (p = 0.26). Grade 2 and Grade 3 thrombocytopenia was significantly seen more in Arm B compared to Arm A. 05 (15.63%), and 01 (3.12%) patients in Arm A and 07 (21.88%) and 04 (12.5%) in Arm B developed Grade 2 and 3 thrombocytopenia. The finding was statistically insignificant (p = 0.43).

Table 11 showed explores the various acute non-hematological toxicities observed between the two arms from the start of the treatment up to 18 weeks following the completion of the treatment. Incidence of nausea and vomiting was almost similar on both arms. 9(28.1%) and 5(15.6%) patients in Arm A whereas 8 (25%) and 3 (9.4%) patients in Arm B developed grade 2 and grade 3 nausea and vomiting. The finding was statistically insignificant (p = 0.46). The incidence of diarrhoea was predominant Arm A. Grade1 and Grade 2 diarrhoea was 15(46.9%), and 7(21.9%) patients in Arm A whereas 6(18.8%) and 0(0%) in Arm B developed Grade 1 and 2 diarrhoea respectively. The finding was statistically significant (p =

Table 11: Overall acute non-hematological toxicities observed during chemotherapy (N = 64).

Toxicities	Arm A (n = 32)	Arm B (n = 32)	Overall (N = 64)	Chi-square test	P-value
Nausea/vomiting					
No	2(6.3%)	6(18.7%)	8(12.5%)	2.59	0.46
Grade 1	16(50%)	15(46.9%)	31(48.4%)		
Grade 2	9(28.1%)	8(25%)	17(26.6%)		
Grade 3	5(15.6%)	3(9.4%)	8(12.5%)		
Diarrhoea					
Grade 0	9(28.1%)	26(81.3)	35(54.7%)	20.11	<0.001
Grade 1	15(46.9%)	6(18.8%)	21(32.8%)		
Grade 2	7(21.9%)	0(0%)	7(10.9%)		
Grade 3	1(3.1%)	0(0%)	1(1.6%)		
Acute kidney injury					
Grade 0	24(75%)	22(68.75%)	46(71.9%)	1.96	0.37
Grade 1	7(21.9%)	6(18.75%)	13(20.3%)		
Grade 2	1(3.1%)	4(12.5%)	5(7.8%)		
Febrile neutropenia					
Grade 0	22(68.75%)	17(53.1%)	39(60.9%)	3.14	0.21
Grade 3	9(28.125%)	15(46.9%)	24(37.5%)		
Grade 4	1(3.125%)	0(0%)	1(1.6%)		
Alopecia					
Grade 0	28(87.5%)	5(15.6%)	33(51.6%)	34.59	<0.001
Grade 1	4(12.5%)	14(43.8%)	18(28.1%)		
Grade 2	0(00%)	13 (40.6%)	13(20.3%)		
Neuropathy					
Grade 0	9(28.12%)	4(12.5%)	13(20.31%)	2.43	0.30
Grade 1	16(50)	20(62.5%)	36(56.25%)		
Grade 2	7(21.88)	8(25%)	15(23.44%)		

<0.001). Grade 2 acute kidney injury depicted to be more in Arm B compared to Arm A. 1(3.1%) patients in Arm A and 06 (18.75%%) in Arm B developed Grade 2 acute kidney injury. The findings were statistically insignificant (p = 0.37). Grade 3 febrile neutropenia was seen to be more in Arm B than Arm A. 09 (28.12%) patients in Arm A whereas, 15(46.9%) in Arm B developed grade 3 febrile neutropenia respectively. Grade 1 and 2 Alopecia was more in Arm B i.e., 14 (43.8%) and 13(40.6%) respectively whereas 04 (12.5%) patients developed grade 1 and no one developed grade 2 alopecia in Arm A. It was seen that overall grade 1 neuropathy was higher in the Arm B i.e., 21 (65.62%) than Arm A i.e., 16 (50%) and grade 2 neuropathy was also higher in Arm B than Arm A i.e., 08 (25%) vs 07 (21.88%) respectively. These findings were statistically insignificant between the two arms (p = 0.30).

Discussion

Patients fulfilling the inclusion criteria were enrolled in this study from different centers of Bangladesh. The mean age of the patient at diagnosis in this study was 57.25 ± 9.62 in Arm A and 56.44 ± 8.61 in Arm B. The overall mean age was 56.84 ± 9.01within the age range of 34-70 years. These finding nearly correlates with El-Helw., *et al*. (2008) [12] where they as well observed the median age of 66 years with the age range of 25-87 in both arms. Among 64 patients, 47 (73.5%) patients were male and only 17 (26.5%) patients were female. The male and female ratio was 2.81. This observation correlates with the study of Kabir, Connolly and Clancy, (2008) which showed a slightly higher incidence in males than females (34% vs 22%). Depending on literacy, it was observed that more than 90% of the patients in both were literate. Majority of patients on the either arm was farmer i.e., 12(37.5%) in arm A and 10 (31.25%) in Arm B. At presentation, most of the patients in both arms had an ECOG performance score of 1 (47% in Arm A and 59% in Arm B), followed by ECOG 2 (37% in Arm A and 35% in Arm B). Multiple risk factors were analyzed. Smoking is the leading cause of lung cancer worldwide. In this study, 25 (78.12%) patients of Arm A and 23 (71.88%) patients in Arm B were smokers. So, in the

total study population, 48 (75%) patients were smokers. Smoking has been defined as the most decisive risk factor for small cell lung cancer (American Cancer Society, 2019). Here, smoking was defined as inhaling the smoke of burning tobacco encased in cigarettes, pipes, and cigars. But many of the study populations also used tobacco in a different form, such as jarda, gul and tobacco leaf. Other risk factors like preexisting lung disease like COPD, Asthma, and TB were also present in few populations in both arms, Arm A 09 (28.12%), 5(15.63%), 4(12.50%) versus Arm B 11 (34.38%), 06 (18.75%), 02(6.25%). The finding was statistically insignificant p>0.05. Overall, the most common presentation was cough 54 (84.38%) followed by dyspnea 28(77.78%). In Arm A, cough was present in 28 (87.5%) followed by dyspnea 12(37.5%) and was the most common presentation, whereas, in Arm B, the most common manifestation was also cough 26(81.25%) followed by dyspnea 16(50%). Other symptoms such as infection 27(42.19%) haemoptysis 17(26.56%), chest pain 13 (20.31%), SVCO 14(21.88%), loss of weight and appetite were present in 22(34.38%) patients. This presentation was similar to the finding by Caballero Vázquez., *et al*. (2020) [13], where they found cough followed by chest pain and dyspnea as a predominant finding. Treatment was started as planned. Dose calculation was done based on the BSA. At least, 95 percent of the calculated dose was given to the patient. The mid-term evaluation was done after the completion of 3 cycles of chemotherapy to find out the response of the population. Partial response was seen in the majority of the patient, 20(62.5%) in Arm A and 21(65.63%) in Arm B. ORR (i.e., CR +PR) was seen in 25(78.13%) in Arm A and 27 (84.38%) in Arm B. The findings were insignificant and this shows that non-inferiorism of Arm A over Arm B, p = 0.80. 1st follow up was done after 6 weeks of completion of the chemotherapy. It was seen that a good number of patients in either arm achieved complete response, 15(46.9%) in Arm A and 19(59.4%) in Arm B. In Arm A, 11(34.4%) patients had a partial response and 4(12.5%) patients had stable disease, whereas 9(28.1%) and 3(9.4%) patients had a partial response and stable disease respectively in Arm B. The findings were statistically insignificant p = 0.76. The response attained at 6 weeks and 12 weeks after chemotherapy were compared among smokers and non-smokers in both Arms. During first follow up it shows that a good number of complete response was seen among non-smokers than smokers 87.5% vs 41.7%. Patients who had partial response and stable disease was found more among smokers than nonsmokers the finding was statistically significant (p = 0.002). Findings of second follow up also attained similar results and the p value was 0.02. These finding supports the finding of Tsao., *et al*. (2006) [14] where they non-smokers had higher response rates (19% vs. 8% vs. 12%; p = 0.004) and lower rates of progressive disease (49% vs. 65% vs. 66%; p = 0.002) than former and current smokers, respectively. 2nd follow up was done 12 weeks after the completion of the treatment. 11(34.4%) patients in Arm A and 14(43.7%) patients in Arm B had complete responses. In Arm A, 8(25%) and 13(40.6%) patients had partial and progressive disease respectively whereas, in Arm B, 7 (21.9%) patients had partial response and 11 (34.4%) patients had progressive disease. The p value was 0.74 which shows that Arm A and B has no difference in the clinical response at 2nd follow up. Both hematological and non-hematological toxicities were assessed. Regarding the acute hematological toxicities, anaemia, thrombocytopenia and leucopenia were commonly observed. Grade 1 anemia was more prevalent in Arm A, 16(50%) whereas grade 2 anaemia is more in Arm B 18(56.25%). The finding was not statistically significant (p = 0.28). This finding supports the study done by Y. Shi., *et al*. (2015), where they as well-found anaemia more in the etoposide-cisplatin regimen regimen than irinotecan-cisplatin (31.3% vs 30%), although the findings were statistically insignificant (p = 0.28). No patients were spared from leucopenia. Most of the patients suffered from grade≥ 2 leucopenia in either arms. 20 patients (62.5%) in Arm A and 25(78.12%) patients in Arm B suffered from grade≥ 2 leucopenia. The finding was statistically insignificant (p = 0.26). This finding correlates with the study done by Kim., *et al*. (2019) [9] where they found WHO grade 2 or more leucopenia in 62.3% vs 71% of a patient (p = **0.26**). Grade ≥ 2 thrombocytopenia was common in Arm B than Arm A 11(34.38%) vs 6 (18.75%). Non-hematological toxicities were also assessed in both the arms. Most commonly noted are nausea/vomiting, diarrhoea, acute kidney injury, febrile neutropenia, alopecia, peripheral neuropathy. No patients were spared from nausea and vomiting. It was seen that 16 (50%) patients in Arm A and 15 (46.9%) patients in Arm B had grade 1 nausea and vomiting. The highest grade of nausea, i.e., Grade 3 was seen in 5(15.6%) patients of Arm A and 3(9.4%) patients of Arm B. Diarrhoea is a more common toxicity of Irinotecan. In our study 23(71.9%) out of 32 patients in arm A developed grade≥ 1 diarrhoea whereas 06(18.8%) out of 32 developed grade 1 diarrhoea only. The finding was statistically significant (p value < 0.001). Cisplatin is a nephrotoxic agent. Proper hydration was ensured before administration of Cisplatin. In our study in Arm A, 7(21.9%) patients had grade 1 toxicity whereas 1(3.1%) patient developed grade 2 toxicity. In Arm B, 6(18.75%) patients developed grade 1 toxicity, whereas 4(12.5%) patients developed Grade 2 toxicity. The finding was statistically insignificant (p = 0.37). In our study, 9(28.125%) patients from Arm A and 15(46.9%) patients from Arm B developed febrile neutropenia. However, the finding wasn't statistically significant (p value = 0.21). Alopecia was most prevalent in arm B. Grade 1 and Grade 2 alopecia was 14(43.8%) and 13(40.6%) in arm B whereas only 04(12.4%) patients in arm A developed grade 1alopecia. The finding was statistically significant (p value < 0.001), It was observed that, Grade≥ 1 neuropathy was found among 23(71.88%) patients of Arm A and 28(87.5%) patients of Arm B. The finding was statistically insignificant (p = 0.30).

Limitations of the Study

It was a non-randomized quasi-experimental study, so selection bias is present. In this time period, overall survival was not possible to be studied. However, this cohort of patients is kept under surveillance to observe those end points.

Recommendations of the Study

Further long-term randomized studies need to be done with multicenter trials to see survival benefits and late toxicities. Studies with larger sample size could help establish the significant benefit in terms of response.

Conclusion

This study supports the fact that Irinotecan-Cisplatin based chemotherapy schedule is not inferior and equally effective in comparison to Etoposide-Cisplatin based chemotherapy regimen which is the standard regimen for Small Cell Lung cancer. Moreover, Irinotecan-Cisplatin regimen also showed acceptable toxicities.

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