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Outcome of neoadjuvant chemotherapy followed by concurrent chemoradiotherapy versus concurrent chemoradiotherapy alone in non-metastatic locally advanced non-small cell lung cancer – A prospective and randomized study

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ABSTRACT

Background: Sequential chemoradiotherapy and concurrent chemoradiotherapy are two treatment options for locally advanced non-small cell lung cancer (NSCLC). Still there is limited data regarding which is the better treatment option. **Aims and Objectives:** This study is to compare the response rate and toxicity pattern between induction (neoadjuvant) chemotherapy followed by concurrent chemoradiotherapy versus concurrent chemoradiotherapy alone in locally advanced NSCLC patients. **Materials and Methods:** A total of 48 Stage III NSCLC patients were selected for the study and were randomized into two arms with a 1:1 ratio. Patients of ARM-1 received concurrent chemoradiotherapy alone of a total dose of 66Gy/33# over 6 and ½ weeks with paclitaxel (50 mg/m^2) and carboplatin (Area under curve [AUC] 2) once every week. The study arm (ARM-2) received two cycles of induction chemotherapy with paclitaxel (175 mg/m^2) and carboplatin (AUC 6) every 3 weeks and concurrent chemoradiotherapy (same CRT as on ARM-1). **Results:** In our study, overall response rate (Complete response + Partial response) in Arm 1 and Arm 2 was 62% and 71%, respectively. The treatment was very tolerated in our study. A mean follow-up of 12 months by Kaplan–Meier survival analysis showed a statistically non-significant difference in disease-free survival in both arms. Progression-free survival was numerically superior in the induction chemotherapy arm but the difference was statistically non-significant. Acute hematological toxicity was numerically more in the concurrent chemoradiotherapy arm, but statistically not significant. Acute lung toxicity, acute pharynx, and esophagus toxicity were numerically more in the induction chemotherapy arm but statistically non-significant. **Conclusion:** There was no significant difference between induction chemotherapy followed by concurrent chemoradiotherapy and concurrent chemoradiotherapy alone in the present study population.

Key words: Concurrent chemoradiotherapy; Induction chemotherapy; Locally advanced; Lung cancer

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INTRODUCTION

In the year 2020, the second most common cancer is lung cancer with an incidence of 2.2 million (11.4%) new cases and the leading cause of cancer-specific mortality (1.8 million death, 18%).[1] About half of patients with non-small cell lung cancer (NSCLC) are in the locally advanced stage (IIIA and IIIB), and even after the best treatment results in a dismal prognosis.[2] In the past, the standard treatment for most Stages IIIA and IIIB was radiotherapy or surgery alone. For patients with N2 diseases at diagnosis or favorable patients with medically inoperable, or unresectable, locally advanced NSCLC, the preferred treatment is platinum-based chemotherapy administered concurrently with RT. The newer therapeutic approaches to combined modality treatment of locoregionally advanced inoperable NSCLC are sequential chemoradiotherapy (induction chemotherapy followed by standard radiation therapy), concurrent chemoradiotherapy, and improvement in radiation technique, dose delivery, and intensified schedules. Several studies were conducted in which sequential chemoradiotherapy was compared with concurrent chemoradiotherapy.[3-6] Concurrent cisplatin-based chemoradiation demonstrated a clear survival benefit at the expense of increased acute toxicity especially severe esophagitis[7] An emerging problem in Stage III disease treated with concurrent chemoradiotherapy is the development of distant metastases that account for the majority of death, some of them occur at this stage due to locoregional failure in the thorax.[8] Adding two cycles of cisplatin-based induction chemotherapy to radiotherapy demonstrated a prolongation of median survival.[9-11] It is seen that concurrent chemoradiotherapy is superior to a single modality of therapy.[12-13] Induction chemotherapy may improve systemic control and concurrent chemotherapy appears to increase locoregional control. Several studies explored the administration of more intensive doublet chemotherapy as induction chemotherapy and during radiotherapy increase overall median survival time than previously achieved with induction (neoadjuvant) chemotherapy alone.[14,15]

Aims and objectives

The present study aims to compare the response rate and toxicity pattern between induction chemotherapy followed by concurrent chemoradiotherapy versus concurrent chemoradiotherapy alone in locally advanced non-metastatic NSCLC patients.

MATERIALS AND METHODS

After obtaining ethical clearance from the Institutional Ethical Committee, a total of 48 Stage III NSCLC patients were selected for study and were randomized into two arms with a 1:1 ratio. Patients of both arms received a total dose of 66Gy/33# over 6 and a ½ weeks and concurrent chemotherapy with paclitaxel (50 mg/m^2) and carboplatin (area under curve [AUC] 2] once every week. The study arm received two cycles of neoadjuvant chemotherapy with paclitaxel (175 mg/m^2) over 3 h and carboplatin (AUC 6) every 3 weeks and concurrent chemoradiotherapy.

ARM-1: Concurrent chemoradiotherapy with weekly paclitaxel (50 mg/m^2) and carboplatin (AUC-2): Concurrent radiotherapy to a dose of 66 Gy at 2 Gy/fraction at five fractions per week.

ARM-2: Two cycles of induction chemotherapy consisted of paclitaxel (175 mg/m^2) with carboplatin (AUC-6) IV every 21 days. Following the completion of induction chemotherapy, concurrent chemoradiotherapy began on day 43 and continued the same as the patient on Arm 1. The differences in response and toxicities between the two arms have been studied and analyzed using SPSS software.

RESULTS

A total of 48 patients were eligible for analysis with 24 patients in Arm 1 and 24 patients in Arm 2. Baseline profiles of the patients in the Arms were comparable in terms of age distribution, sex distribution, pre-treatment performance status, tumor (T) status, nodal (N) status, and histology. The mean ages of patients were (55.48±1.527) years for Arm 1 and (54.96±1.434) years for Arm 2. Hence, age distribution is comparable in both arms (P=0.805). The male patients accounted for 88% in Arm 1 and 95.65% in Arm 2. In Arm 1, the female patient is 12% and in Arm 2, it is 4.34%. Hence, in both arms, sex distribution is comparable (P=0.610). ECOG performance statuses were comparable in both arms (P=0.845). Adenocarcinoma (41.66%) followed by squamous cell carcinoma (39.58%) was the most common type of histology. Histological subtype distribution was also comparable in both arms. In Arm 1, N0, N1, N2, and N3 disease were 8%, 20%, 48%, and 24%, respectively, and in Arm 2, 8.69%, 30.43%, 39.13%, and 21.73%, respectively. Nodal status in both the arm is comparable (P=0.856). In Arm 1, T2, T3, and T4 disease were 16%, 44%, and 40%, respectively, and 21.73%, 47.82%, and 30.43% in Arm 2, respectively (P=0.756). Hence, there was no significant difference in according to tumor status (T) between the two arms. The mean months of follow-up of patients were (8.04±0.729) months for Group 1 and (8.22±0.827) months for Group 2 (P=0.872).

Response assessment

Forty-eight patients were evaluated for response at stipulated 6–8 weeks post-treatment using RECIST criteria. The overall response rate (Complete response+Partial response [PR]) in Arm 1 was 62% and in Arm 2 was 71%. Progressive disease (PD) was seen in 24% (six patients) in Arm 1 and

13.04 % (three patients) in Arm 2 (Figure 1 and Table 1). This difference was statistically not significant (P=0.759).

Recurrence

Among the CR patients, the disease recurred in 40% of patients in Arm 1 and 16.66% in Arm 2 (Table 2). It is seen that the numerical recurrence rate in Arm 1 is higher but statistically non-significant (P=0.545).

Disease-free survival (DFS)

During follow-up, it had been found that there was no statistically significant difference in DFS in both arms (Log Rank Test P=0.932). The mean DFS was 9.467±1.336 months in Arm 1 (95% confidence interval (CI) 6.847–12.086) and 10±1.732 months in Arm 2 (95% CI 6.605 to 13.395) (Figure 2).

Progression of disease in patients who had PR or SD

Progression of disease was seen in 42.85% of cases with PR or SD in Arm 1 and 28.57% of cases in Arm 2 patients (Table 3) (P=0.695).

Comparison of progression-free survival (PFS) in patients who have a PR or stable disease (SD) after treatment (PFS) (Figure 3)

During the follow-up, disease progression occurred in 6 (42.85%) patients out of 14 partial responders (PR) and SD in Arm 1 (mean time to progression of 10.36±1.31 months in compared to 4 (28.57%) patients out of 14 in Arm 2 (mean time to progression (11.81±1.31 months). Hence, PFS is numerically superior in the induction chemotherapy arm (Arm 2). Although this difference was not statistically significant [log rank test P=0.412.

Acute toxicities

Grade 1 and 2 acute hematological toxicities in Arm 1 were 37% and 17%, respectively, and in Arm 2, 37% and 9%, respectively. One patient in Arm 1 had Grade 3 toxicity. They have managed accordingly. Acute hematological toxicity in both arms was comparable (P=0.496). Acute lung toxicity of Grade 1 and 2, respectively, was 37% and 17% in Arm 1 and 50% and 17% in Arm 2. Moreover, it managed conservatively. The difference is not statistically significant (P=0.524). In Arm 1, Grade 1 Pharynx and Oesophagus toxicity was observed in 12 patients, and Grade 2 toxicity in three patients. In Arm 2, Grade 1 toxicity was observed in 12 patients, Grade 2 in five patients, and Grade 3 toxicity in two patients. No Grade 4 toxicity was observed in any arm. All patients were treated conservatively. The difference between acute pharynx and esophagus toxicity in between the arms was statistically not significant (P=0.44). Acute skin toxicity is mainly due to radiation and chemotherapy enhances this toxicity. In Arm 1, Grade 1 toxicity was seen in five patients and Grade 2 in one patient. In Arm 2, Grade 1 toxicity was observed in four patients. There was no Grade 2 toxicity in Arm 2. There was also no Grade 3 or Grade 4 toxicity in any arm. The toxicity is comparable in both arms (P=0.598). All acute toxicity is summarized in Table 4.

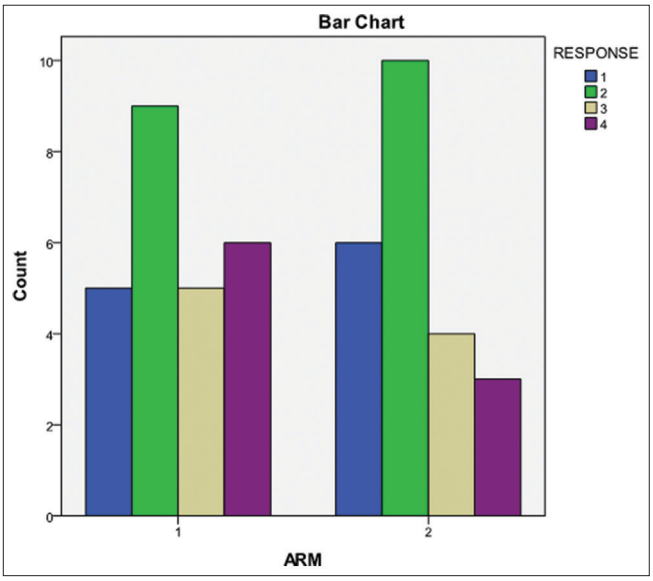

Figure 1: Responses at follow-up after completion of treatment, (1-Complete Response, 2-Partial Response, 3-Stable Disease, and 4-Progressive Disease)

Table 1: Responses at follow-up after completion of treatment (P=0.759)

ARM	Response (%)				Total (%)
	CR	PR	SD	PD	
1	6 (25.0)	9 (37.0)	5 (21.0)	4 (17)	24 (100.0)	48 (100.0)
2	7 (29)	10 (42)	4 (17)	3 (12)	24 (100.0)	
Total	13 (27)	19 (40)	9 (19)	7 (14)		

Pearson Chi-square, CR: Complete response, PR: Partial response, SD: Stable disease, PD: Progressive disease

Table 2: Comparison of recurrence after the complete response (CR) P=0.545 (Fisher's exact test)

ARM	After complete response recurrence yes/no (%)		Total (%)
	No	Yes	
1	3 (60.0)	2 (40.0)	5 (100.0)
2	5 (83.33)	1 (16.66)	6 (100.0)
Total	8 (72.72)	3 (27.27)	11 (100.0)

CR: Complete response

DISCUSSION

Lung cancer is one of the most common malignancies worldwide. Analysis of data from 22 cancer registries in five continents revealed that cumulative lung cancer risks were

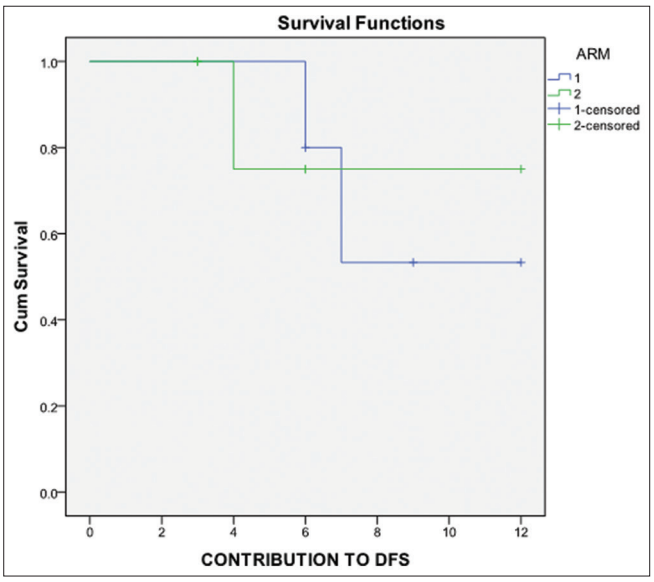

Figure 2: Comparison of disease-free survival

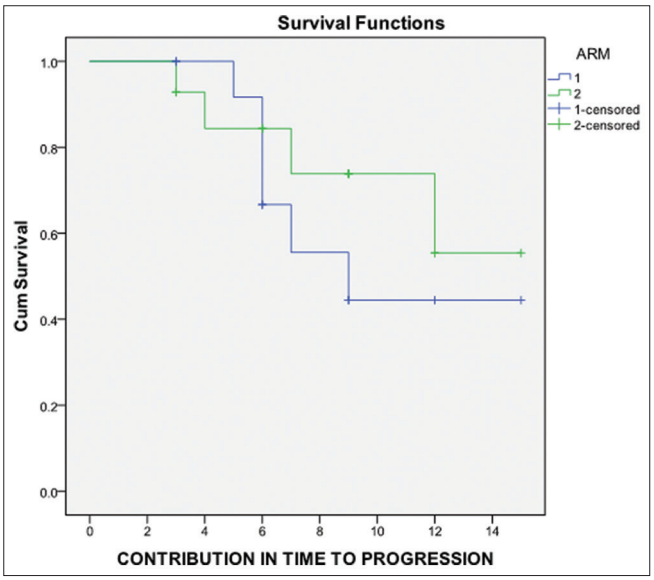

Figure 3: Comparison of time to progression (survival function)

Table 3: A comparison of progression of disease in partial response (PR) or stable disease (SD) cases P=0.695 (Fisher's exact test)

ARM	Progression of patients with partial response or stable disease (%)		Total (%)
	No	Yes	
1	8 (57.14)	6 (42.85)	14 (100.0)
2	10 (71.42)	4 (28.57)	14 (100.0)
Total	18 (64.28)	10 (35.71)	28 (100.0)

higher in males than in females.[16] Approximately 80% of NSCLC in men worldwide is directly attributable to cigarette smoking.[17] These features were also encountered in our study population. The therapeutic approach in unresectable NSCLC is a widely discussed and debatable one. The optimum treatment modality is yet to be defined. In our study, 91.66% of patients were male with mean age of diagnosis (55.48±1.527) years in Arm 1 and (54.96±1.434) years in Arm 2. Among them, 85.41% of patients were smokers. This data are corroborative with the world's incidence of lung cancer in smokers.[18] The patients were diagnosed by computed tomography (CT)-guided fine needle aspiration cytology or bronchoscopic biopsy. Adenocarcinoma (41.66%) followed by squamous cell carcinoma (39.58%) was the most common type of histology.

Induction chemotherapy has several theoretic advantages, including reducing tumor volume, enhancing local control, treatment of micro metastatic disease, and as well as better tolerated. Our study had two arms – Arm 1 – concurrent chemoradiotherapy and Arm 2 – two cycles of induction chemotherapy followed by concurrent chemoradiotherapy. Baseline profiles of both groups were comparable in terms of age and sex distribution, performance status, tumor status, and nodal status.

Our study is an attempt to report our experience with induction chemotherapy followed by concurrent chemoradiotherapy in locally advanced unresectable NSCLC. There are few trials that have reported on the use of induction chemotherapy followed by chemoradiotherapy. A cancer and leukemia Group B (CALGB) trial randomized 366 patients with Stage III NSCLC to immediate chemotherapy (carboplatin, paclitaxel, and 66Gy) or induction chemotherapy with two cycles of carboplatin and paclitaxel before chemoradiotherapy.[19] The necessity to improve the prognosis induction chemotherapy was introduced. The CALGB showed that survival differences were not statistically significant with induction chemotherapy (12 months vs. 14 months, P=0.3). The addition of induction chemotherapy to concurrent chemotherapy added Grade 4 toxicity (24% vs. 41%, P=0.001). Iranzo et al., did a study on Induction chemotherapy followed by concurrent chemoradiotherapy for patients with non-operable Stage-III NSCLC. The overall response rate was 64.6%. It observed Grade 3 and 4 hematological and Grade 2 esophagus toxicity (28.1% cases).[20] The LAMP Phase II and randomized study showed that median survival was higher in the arm receiving concurrent chemoradiotherapy followed by induction chemotherapy (16.3 months vs. 12.7 months). In a Phase II trial with carboplatin/gemcitabine induction chemotherapy followed by radiotherapy concomitantly with paclitaxel/gemcitabine(P/G) in Stage III NSCLC, PR was 74% (28 patients), stable disease (SD) 24% (nine patients), and 2% (one patient) had PD. The toxicity of induction CT was minimal.[21]

In an attempt to improve the prognosis, concurrent chemoradiation was introduced and chemotherapy acts

Table 4: Comparison of acute toxicities

RTOG acute toxicity	ARM	Grade (%)				Total (%)	P-value
		0	1	2	3		
Hematological	1	11 (46)	9 (37)	4 (17)	0 (0)	24 (100.0)	0.496
	2	13 (54)	9 (37)	2 (9)	0 (0)	24 (100.0)	
Lung/pneumonitis	1	11 (46.0)	9 (37.0)	4 (17.0)	0 (0)	24 (100.0)	0.524
	2	8 (33)	12 (50)	4 (17)	0 (0)	24 (100.0)	
Pharynx and esophageal toxicity	1	9 (37)	12 (50)	3 (17)	0 (0)	24 (100)	0.44
	2	4 (17.39)	12 (52.17)	5 (21.73)	2 (8.69)	24 (100)	
Skin	1	18 (75.0)	5 (21.0)	1 (4.0)	0 (0)	24 (100.0)	0.598
	2	20 (83)	4 (17)	0 (0)	0 (0)	24 (100.0)	

as a radiosensitizer. The combination of chemotherapy and radiation may improve the local control and survival rate because of the additive or synergistic effect of chemoradiation.[22] Some of the more encouraging data from concurrent chemoradiotherapy trials in NSCLC have been obtained with regimens that allow for the administration of full-dose chemotherapy during radiation.[23,24] The identification of novel regimens that allow for the administration of systemic doses of chemotherapy during radiotherapy may be feasible using novel cytotoxic agents.[25] In our present study, overall response rate was 69.55% in the induction chemotherapy arm and Iranzo et al., reported a 64.6% overall response rate in a similar study. In between two arms, with respect to response pattern, there was no statistically significant difference.

The treatment was very tolerated in our study. A mean follow-up of 12 months by Kaplan–Meier survival analysis showed a statistically non-significant difference in DFS in both arms (Log Rank test value=0.932). PFS was numerically superior in the induction chemotherapy arm (Arm 2) but the difference was statistically non-significant (Log Rank test value=0.412). Acute hematological toxicity was numerically more in Arm 1, but statistically not significant (P=0.496). Acute lung toxicity, acute pharynx, and esophagus toxicity were numerically more in the induction chemotherapy arm (Arm 2) but statistically non-significant (P=0.524 and 0.44, respectively).

Limitations of the study

Our sample size is small and the duration of the study period is short, so any statistical data have to be interpreted with caution. As the duration of the study was small, analysis of chronic toxicity was not included in the study.

CONCLUSION

The present study was designed to study the difference between responses in the two arms, acute toxicity pattern, DFS, and PFS. Both in terms of responses and acute toxicities, both arms were similar. No statistically significant differences were observed between these two arms. To conclude, there was no significant difference between induction chemotherapy followed by chemoradiotherapy and chemoradiotherapy alone in the present study population. Further studies with larger sample sizes and longer duration of follow-ups are necessary.

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