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COMPARISON BETWEEN CONCOMITANT CHEMO-RADIOTHERAPY WITH CISPLATIN VERSUS INDUCTION CHEMOTHERAPY FOLLOWED BY CONCOMITANT CHEMORADIOTHERAPY WITH CISPLATIN AND ETOPOSIDE REGIMEN IN CASES OF LOCALLY ADVANCED NON –SMALL CELL LUNG CANCER

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ABSTRACT
Background:This study was designed to compare between patients treated with concurrent chemo-radiotherapy with single agent cisplatin and those treated with induction chemotherapy with cisplatin –etoposide regimen followed by concomitant chemo-radiotherapy with cisplatin and etoposide combined regimen.
We randomly assigned 40 patients with biopsy proven locally advanced irresectable non metastatic non small cell lung cancer to one of two treatment. Concurrent conformal chemo-radiotherapy at a dose of 60Gy in 6 weeks with single agent Cisplatin 50 mg/m2 on the first day of each treatment weekly or patient underwent Induction chemotherapy with two cycles of cisplatin [25 mg/m2 on days 1-3] and etoposide [100 mg/m2 on days 1-3] regimen with an interval of 21 days followed by conformal concomitant thoracic irradiation [60 Gy /6weeks] with two more cycles of the same chemotherapy regimen
Results showed that response was significantly improved in the induction group with cisplatin and etoposide as compared with the concurrent chemo-radiotherapy group with single agent cisplatin [P = 0. 014],with median follow up of 18 months,the survival was numerically better in the induction group although it did not reach level of significance,there was significant improvement in progression free survival in the induction arm,mean progression free survival was 11.01 in the induction arm versus 8.06 in the concomitant chemoradiotheapy arm [p= 0. 016]
Conclusion: In locally advanced NSCLC,the induction chemotherapy with cisplatin and etoposide followed by concomitant chemoradiotherapy with the same agents gets significant better overall response and disease free survival than concomitant chemoradirtherapy with single agent cisplatin.

INTRODUCTION

Lung cancer is the leading cause of cancer mortality worldwide, with 1. 2 million global deaths a year. [(1)] It has been the most common cancer worldwide since 1985, both in terms of incidence and mortality. Non–small cell lung cancer (NSCLC) constitutes 85% of lung cancer and it is mainly due to active and passive smoking.[(1)]

Locally advanced un-resectable NSCLC have for a long time been treated with thoracic radiation only. The use of induction chemotherapy followed by radiation had been evaluated in several randomized studies and an improvement in overall survival was demonstrated. Recent trials have shown that concurrent chemo-radiotherapy offers a significant survival advantage compared to radiotherapy alone. Based on these data concurrent chemoradio-therapy become the standard of care for patient with good performance status. [(2)]

Because both induction and concomitant chemo-radiotherapy are superior to radiotherapy alone, it can be postulated that combining sequential chemo-therapy with a concomitant approach could result in a further improvement in treatment outcome over concomitant chemo-radiotherapy alone. This combined modality gives us systemic disease control by the induction chemo therapy and higher locoregional control by concomitant chemoradiation. [(2)]

The objective of our study is to compare induction chemotherapy followed by concomitant radio chemotherapy in locally advanced NSCLC with concomitant chemo-radiotherapy alone.

MATERIAL AND METHODS

Eligibility criteria
Eligible patients were ones with biopsy proven locally advanced un-resectable NSCLC, stage IIIA,IIIB and IIIC. Age of the patient must be above 18 and below 75. Performance status, must be 70% or more

according to Karnofisky scale. (3)Adequate kidney function and cardiac function tests .

Treatment plan

The pretreatment evaluation of eligible patients included complete history, physical examination, routine laboratory tests, pulmonary fuction tests and electro-cardiography . To exclude metastatic disease, bone scan, ultrasound or C.T abdomen were done .C.T brain was done in patients with suspected brain deposits.

This study was carried out on 40 patients with locally advanced NSCLC divided into two groups .Group I: It included twenty patients received concomitant chemo-radiotherapy with single agent Cisplatin 50 mg/m2 weekly for 6 weeks. Radiotherapy with standard dose conformal radiotherapy (3 dimension conformal radiotherapy) 40-45 Gy were delivered to the clinical target volume [CTV], followed by a boost to gross tumor volume [GTV] to a total dose of 60 Gy. Group II: It included twenty patients, who received induction chemotherapy with two cycles of cisplatin –etoposide regimen with an interval of 21 days in the following doses: cisplatin 25 mg/m2 on days 1-3, etoposide 100 mg/m2 on days 1-3. followed by Concomitant chemo-radiotherapy with two cycles of the same regimen of cisplatin –etoposide combined with the same radiotherapy schedule

STATISTICAL ANALYSIS:

The Data was collected and entered into the personal computer. Statistical analysis was done using Statistical Package for Social Sciences (SPSS/version 21) software. for categorized parameters Monte Carlo test was used. The level of significant was 0.05.

RESULTS

Response

In group two after induction chemotherapy, response was assessed in twenty patients after receiving induction chemotherapy with cisplatin and etoposide. 6 patients had partial response [30 %], no patients had complete response, 3 patient had progressive disease [15%] and eleven patients had stable disease [55%]. (Table 1)

At the end of concomitant treatment: response rate was significantly improved in the induction arm with doublet chemotherapy cisplatin and etoposide [p = 0. 014]. None of patients had complete response in the arm with concomitant single agent cisplatin. While, 20% of the patients had complete response in the induction arm, stable disease was 15 % in the induction arm and 30% in the concomitant chemoradiation arm. Progressive disease was 20% and 5 % in the concomitant and induction arm respectively. (Table 2)

A multivariate analysis of response with gender, age, performance scale, histological types and clinical stage showed that there was a significant correlation between response and performance status in both groups, good performance status was a good indication of good response in both groups, clinical stage of disease affected response significantly in both group as well, late clinical stage correlated significantly with poor response. (Table 3 and 4)

Survival

Analysis was performed after a follow up period of 18 months, there was a survival difference between the two studied groups, survival was numerically better in the induction group although it did not reach level of significance, [p=0.211] (Fig 1). The mean overall survival in group 1 was 10.8 months. While in group 2, it was 12.01 months. . A multivariate analysis of survival with gender, age, performance scale, histopathological types and clinical stage showed that there was a notable correlation between overall survival rate and clinical stage in both groups. Late clinical stage had significantly worse survival rate. Performance status affected survival significantly in both groups as well. Late clinical stage and low performance status were confirmed as bad prognostic factors.

Progression free survival was significantly improved in induction arm [p= 0. 016]. The mean progression free survival was 11. 1 months in the induction group versus 8.06 months in the concurrent arm. Patients were classified according to the type of first recurrence, whether local failure, distant metastasis or both of them. The main reason for progression in both groups was distant metastasis [40% in the concomitant chemoradiotherapy alone arm versus 30% in the induction arm] (Table 5)

Toxicity

Toxicities of the treatment were generally within an acceptable level and comparable between two groups, Esophagitis was the most common radiation toxicity in both groups, it was comparable in the two groups. Neutropenia was the most common chemotherapy toxicity, it increased significantly in the induction arm.

Table (1): Response at the end of induction chemotherapy in group II

Response	Group II "n=20"	
	No	%
Complete response	0	0.0
Partial response	6	30.0
Stable disease	11	55.0
Progressive disease	3	15.0

Table (2): Response at the end of treatment.

Response	Group I "n=20"		Group II "n=20"		Total "n=40"	
	No	%	No	%	No	%
Complete response	0	0	4	20	4	10.0
Partial response	10	50	12	60	22	55.0
Stable disease	6	30	3	15	9	22.5
Progressive disease	4	20	1	5	5	12.5
MC	9.85					
P-value	0.014*					

MC = Monte Carlo test

Table (3): The association between the performance status and the clinical stage of disease with response of disease in group I.

Performance status	Total	Complete response		Partial response		No response		Progressive diseases		(MC) P-value
Group I		No.	%	No.	%	No.	%	No.	%	
Performance status										
100%	1	0	0.0	1	100	0	0	0	0	17.32
90%	5	0	0.0	5	100	0	0	0	0	0.001*
80%	11	0	0.0	4	36.4	6	54.5	1	9.1	
70%	3	0	0.0	0	0	0	0	3	100	
Clinical stage										
III A	14	0	0.0	9	64.3	5	35.7	0	0	15.66
III B	5	0	0.0	1	20.0	1	20.0	3	60.0	0.001*
III C	1	0	0.0	0	0	0	0.0	1	100.0	
Total		**0**		**10**		**6**		**4**		

MC = Monte Carlo test

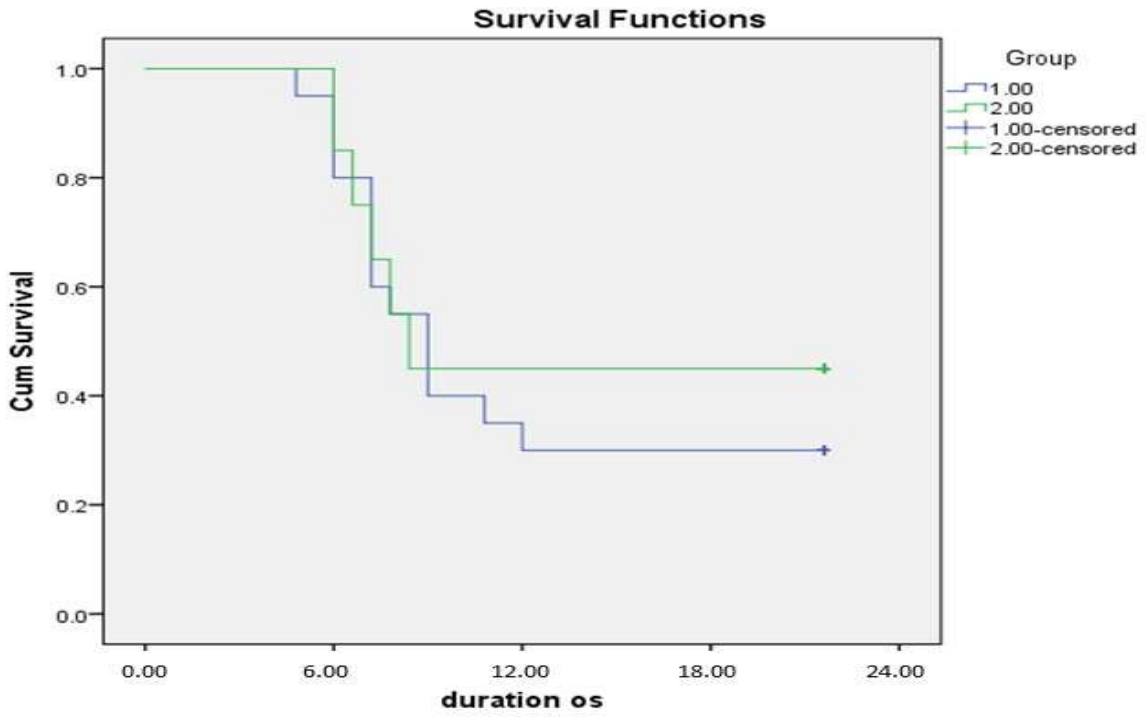

Fig.(1): Kaplan Maier curve for comparison between the two studied groups regarding over all survival.

Table (4): ***The association between the performance status and the clinical stage of disease with response of disease in group II.***

Performance status	Total	Complete response		Partial response		No response		Progressive diseases		MC P-value
Group II Performance status										
100%	2	2	100.0	0	0.0	0	0	0	0	
90%	5	2	40.0	3	60.0	0	0	0	0	10.9
80%	9	0	0	9	100.0	0	0	0	0	0.016*
70%	4	0	0	0	0.0	3	75.0	1	25.0	
Clinical stage										
III A	15	4	26.٧	11	73.	0	0	0	0	11.2
III B	4	0	0	1	25.0	3	75.0	0	0	0.011*
III C	1	0	0	0	0.0	0	0	1	100	

MC = Monte Carlo test

Table (5): Comparison between the two studied groups regarding progression free survival.

	Group I (N=20)		Group II(N=20)	
	No.	**%**	**No.**	**%**
At base line	20	100.0	20	100.0
3 months	18	90.0	19	95.0
6 months	12	60.0	17	85.0
9 months	10	50.0	16	80.0
12 months	9	45.0	14	70.0
15 months	8	40.0	12	60.0
18 months	6	30	11	55.0
The mean PFS (months)	8.06		11.10	
MC	3.65			
p	0.016*			

MC = Monte Carlo test

DISCUSSION

Our current study was based on the observation that both sequential chemoradiotherapy and concomitant chemoradiotherapy have superior response and longer survival that radiotherapy alone in treatment of locally advanced NSCLC, based on the result of CALGB study 8433[4] and the EORTC results.[5] which demonstrated that cisplatin concurrent with radiotherapy significantly improved both locoregional control and survival compared with radiotherapy alone, two meta-analyses reported that both sequential chemoradiotherapy and concomitant proved a benefit over radiotherapy alone.[6]

A meta-analysis on 1,205 patients with unresectable locally advanced NSCLC confirmed that, compared to sequential chemoradiotherapy, concomitant chemo-radiotherapy improves 5 – years survival from 10.6% to 15.1% (P = 0.004). Two – years survival was 30.3% and 35.6% respectively.[7] The question on the potential benefit of induction chemotherapy preceding a concomitant chemoradiotherapy remains unanswered.

In the present study, we examined combining sequential chemotherapy with concomitant chemoradiation and compared it with concomitant chemo-radiation. Our finding confirmed this observation, the response rate was significantly improved in the induction arm, it was 80% [60% partial response and 20% complete response] versus 50% in the group with concomitant chemoradiotherpy alone [50% partial response, 0% complete response]. In 2002, Vokes *et al*,[8] conducted a phase II trial with three different induction chemotherapy regimen [cisplatin with gemcitabine or paclitaxel or vinorelbine] followed by concomitant chemoradiotherapy with the same regimen, response rates at the end of the treatment were 74%, 67% and 73% respectively. In a phase 2 study by Lerouge D *et al*,[9] 70% of patients were included to receive induction chemotherapy with cisplatin and vinorelbine followed by the same chemotherapy regimen concomitant with radiotherapy. Overall response rate was 50% with 7.14% complete response and 38.57% partial response.

In phase 2 prospective study of Patel SH *et al*,[10] to evaluate the result of the treatment of 37 patients with induction chemotherapy with carboplatin and vinorelbine followed by concomitant topotecan and accelerated radiotherapy in locally advanced NSCLC, the study showed an overall response rate of 71%, complete response was 14% and partial response was 57%.

A phase I & II study by Liu D *et al*,[11] whose study tested the addition of cetuximab to induction chemotherapy consisted of vinorelbine and cisplatin followed by concurrent cetuximab, vinorelbine, cisplatin and thoracic radiation, the overall response rate was 63%, 77.8% after the induction and concomitant respectively chemoradiotherapy respectively.

The present study, the mean overall survival wasnumerically better in the induction chemotherapy arm but it did not reach the level of significance, it was 12.01 month for the induction arm versus 10.8 month for concomitant chemoradiotherapy.

The one year survival rate was (80% and 60%) in the induction arm and concomitant chemoradiotherapy arm respectively. The 18 month survival was 65% in the induction arm versus 50% in the concomitant chemoradiotherapy arm. Vokes *et al*,[8] study achieved one-year survival rates in the three induction chemotherapy arms with (gemcitabine, paclitaxel and vinorelbine) (68%, 62% and 65% respectively).

Patel SH *et al*,[10] showed a median survival of 17.9 months, overall survival at 1, 2 and 3 years was 62%, 41% and 33% respectively, the 5 year survival was 21%, Liu D et al,[11] study achieved median survival of 26.7 months, one and two years survival rates of 88.9% and 51.9% respectively.

A recent 2016 retrospective cohort study by Ahmed *et al*,[12] to investigate survival benefit of carboplatin based induction chemotherapy before modern day concurrent chemo-radiotherapy compared to concurrent chemo-radiotherapy without induction, results showed that induction chemotherapy significantly improved all survival.

Overall one and two year survival rates were 76.7% and 53.3% in the induction group while there were 60% and 18.7% in the concurrent group. Univariate analysis exposed older age [p = 0.01], greater tumor volume [p= 0.03] and squamous cell pathology [p = 0.02] as negative prognostic factors in overall survival. In the present study, late clinical stage and low performance status were confirmed as a bad prognostic factors.

The present study the progression free survival was significantly longer in the induction arm (11.1 months) versus (8.06) in the current chemoradiotherapy alone arm (p= 0.016), the main reason of progression was mostly because of distant metastasis in both groups, the median disease free survival in the three induction chemotherapy arm (gemcitabine, paclitaxel and vinorelbine) in Vokes *et al*,[8] study were 8.4 months, 9.1 month and 11.5 months respectively.

The median time to first relapse was 12.2 month in Patel SH. *et al*,[10] study. While in Liu D *et al*[11] study, median progression free survival was 13.5 months, Ahmed et al[12] study as well also showed that induction chemotherapy significantly improved progression free survival and distant metastasis free survival.

From the present study it could be concluded that in locally advanced NSCLC, the induction chemotherapy with cisplatin and etoposide followed by concomitant chemoradiotherapy with the same agents gets significant better overall survival and disease free survival than concomitant chemoradirtherapy with single agent cisplatin.

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