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A PROSPECTIVE COMPARATIVE STUDY BETWEEN CONCURRENT CHEMO RADIOTHERAPY WITH CISPLATIN AND ETOPOSIDE VERSUS PACLITAXEL AND CARBOPLATIN IN LOCALLY ADVANCED NON SMALL CELL LUNG CARCINOMA

Oncology/Radiotherapy

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ABSTRACT

Background-The current standard of treatment for unresectable locally advanced Non-small cell lung carcinoma is radiation with concurrent platinum based doublet chemotherapy. But there remains considerable debate over the optimal concurrent regimen , with some advocating Cisplatin-Etoposide , others prefer carboplatin-paclitaxel as an equally effective and better tolerable concurrent regimen.. With this background, our study was aimed at comparing loco-regional control and toxicity profile between these two regimens.

Material And Methods- Locally advanced non-metastatic Non-small cell lung carcinoma patients were randomized in two groups- study group received External beam radiotherapy(60Gy/30 fractions/6 weeks) in conventional fractionation along with concurrent weekly chemotherapy with Inj.paclitaxel (45 mg/m2) and Inj. Carboplatin (AUC2) and control group received same radiotherapy dose with concurrent Inj.cisplatin (50mg/m2) Day 1,8,29,36 and Inj.Etoposide (50 mg/m2) Day 1-5 and Day 29-33. After treatment completion , Locoregional Tumor response was assessed . Patients were evaluated weekly for acute toxicity during radiation therapy, then once at 6-8 weeks after completion of treatment and thereafter every three months for at least 6 months.

Results- Overall treatment Response in Study Arm was higher than control arm (73% vs 70%). Complete response rate was also higher in study arm (40% vs 30%) though these differences were not statistically significant [p value 0.701]. Although statistically not significant ,Grade III haematological toxicity was less (3% vs 6%) in study arm .Other toxicity profiles including acute lung, esophageal and skin toxicities are comparable in both the arms of the study.

Conclusion- Concurrent chemo- radiotherapy with cisplatin -etoposide versus paclitaxel -carboplatin in locally advanced NSCLC are comparable in terms of loco-regional control and acute toxicity.

KEYWORDS

NSCLC , concurrent chemoradiotherapy, etoposide-cisplatin, paclitaxel-carboplatin.

INTRODUCTION

According to GLOBOCAN 2020 Lung Cancer is the fourth most common cancer (5.5% of all cancer cases) in India.[1] Non–small-cell lung cancer (NSCLC) accounts for 80% of all lung cancer cases.[2]Only 15% of NSCLC patients present with localized disease, the rest have either lymph node metastasis(25%) or distant metastasis(65%) at the time of diagnosis.[3]The current standard of care for patients with unresectable locally advanced NSCLC is radiation with platinum based doublet chemotherapy concurrently.[4] The NSCLC Collaborative Group meta- analysis and the meta-analysis of platinum-based concomitant chemotherapy in NSCLC demonstrated that adding sequential or concomitant chemotherapy to radical radiotherapy improved survival in locally advanced NSCLC.[5,6] Several NSCLC trials and meta- analysis have compared sequential and concomitant combinations directly, almost all of which showed a trend favouring concomitant chemoradiotherapy at the cost of increased toxicity.[5,6]But there remains considerable debate over the optimal regimen for this disease, with some practitioners believing that Cisplatin-Etoposide is more effective, especially when the goal of treatment is cure, while others feel that carboplatin-paclitaxel is equally effective for stage III NSCLC and is potentially better tolerated.

With these results in the background, we performed a prospective comparative study to compare loco-regional control and toxicity profile of Chemo-Radiotherapy with Cisplatin and Etoposide Versus Chemo- Radiotherapy with Carboplatin and Paclitaxel in locally advanced Non-small cell lung carcinoma.

MATERIALS AND METHODS

It was a double arm, prospective, Comparative, single institutional study done among the patients with locally advanced Non-small cell lung carcinoma aged between18-70 years, having adequate hepatic, renal, haematological parameters and a ECOG score of 0-2 , without any associated co-morbidity. Patients with recurrent lung carcinoma,previous history of any other malignant disease or chemotherapy or radiotherapy were excluded from the study. This study was performed between June 2020 and June 2021.

Study Technique:

Patients were randomly allocated in two groups.

CONTROLARM-

Patients of control arm received EBRT at a dose of 60 Gy/30 fractions /6 weeks in conventional fractionation along with concurrent chemotherapy with Inj. Cisplatin (50mg/m^2) Day 1,8,29,36 and Inj. Etoposide (50mg/m^2) D1-5 and D29-33.

STUDY ARM-

Patients in study arm received Radiotherapy at a dose of 60 Gy/30 fractions/6 weeks with concurrent weekly Inj. Paclitaxel (45mg/m^2) and Inj. Carboplatin (AUC2).

RADIOTHERAPY TECHNIQUE-

Total dose of RT was 60 Gy at 2 Gy/fraction, 5 fractions /week for 6weeks for both the arms. Target volumes were taken as following-

GTV includes Gross Tumour and Nodes

CTV=GTV+8mm Margin

PTV=CTV+10 -15mm Superior/ inferior and at least 10mm margin in axial plane

OARs include Normal Lung, Heart, Spinal Cord, Oesophagus.

After completion of treatment, Locoregional Tumor Response was assessed by RECIST v.1.1 . The changes of BSA(Body surface area) observed during treatment and dose of drugs were adjusted according to this changes. Treatment related acute toxicities were evaluated during weekly follow-up visits when the patient was under radiation treatment using RTOG criteria.

Treatment related toxicities were managed accordingly. Patients were evaluated weekly for acute toxicity during radiation therapy, then 6-8 weeks after completion of treatment and thereafter every three months for at least 6 months based on clinical status, biochemical and radiological parameters.

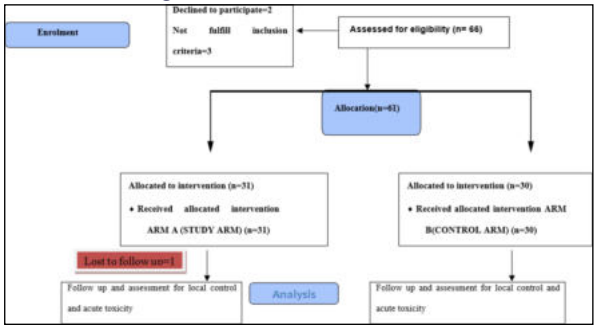
There is no source of financial grant or other funding.

Statistical Analysis-

Data was analyzed and compared according to appropriate statistical tests using SPSS v.20 software and microsoft word-excel. Data was summarized as mean and standard deviation for numerical variables and count and percentages for categorical variables. Unpaired proportions were compared by Chi-square test or Fisher's exact test, as appropriate. Any p value < 0.05 will be considered statistically Significant.

RESULTS

Consort Flow Diagram



Total 60 patiens were analysed in the two arms of the study. Both the arms were comparable in terms of age, gender, pre-treatment performance status, T and N stage of the disease at the time of presentation and history of smoking**.**

Table1.Distribution Of Baseline Characteristics Between Two Arms Of The Study.

CHARACTERISTICS		ARM OF THE STUDY		TOTAL SAMPLE SIZE	P-VALUE
		CONTROL ARM (n=30)	STUDY ARM (n=30)		
MEAN AGE (in years)		56.23	53.8	60	0.73
GENDER	MALE	25	26	60	0.718
	FEMALE	5	4		
	TOTAL	30	30		
ADDICTION TO SMOKING	SMOKER	25	27	60	1.0
	NON-SMOKER	5	3		
	TOTAL	30	30		
TUMOUR (T) STAGE	T2 T3 T4	4 16 10	6 14 10	60	0.766
	TOTAL	30	30		
NODAL (N) STAGEg	N0 N1 N2 N3	0 9 13 8	1 7 14 8	60	0.732
	TOTAL	30	30		
PERFORMANCE STATUS(ECOG Score)	0 1 2	02 14 14	03 15 12	60	0.824
	TOTAL	30	30		

Adenocarcinoma is the most common histology found in both the arms of study.26 % of control arm and 30% of study arm patients have histological diagnosis of adenocarcinoma.Squamous cell carcinoma is the second most common variety of histology (20% vs 15%) in both the arms though this difference is statistically insignificant.

Table2. Distribution Of Histological Variants Of NSCLC Between Both The Arms

ARM OF STUDY	TUMOUR HISTOLOGY				TOTAL	P-VALUE
	ADENOCARCINOMA	BRONCHOALVEOLAR	LARGE-CELL	SQUAMOUS CELL		
STUDY CONTROL	18 16	1 2	2 0	9 12	30 30	0.236
TOTAL(N)	34	3	2	21	60	

Overall treatment response (Complete response+Partial response) in Study Arm was higher than control arm (73% vs 70%). Complete response rate was also higher in study arm(40% vs 30%). But,these differences were not statistically significant [p value 0.701].

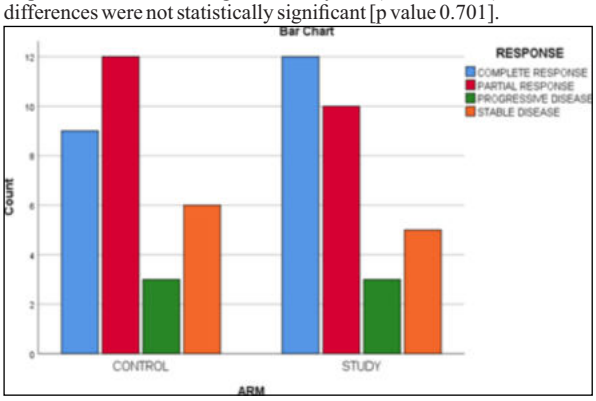


Figure -1. Responses After Completion Of Treatment In Both Arms Of Study

Grade III haematological toxicity was higher (6% vs 3%) in control arm containing Etoposide and cisplatin as concurrent chemotherapy. 46% of patients in study arm had no haematological toxicity than 26 % of control arm. But, these differences were not statistically significant (p-value 0.236).

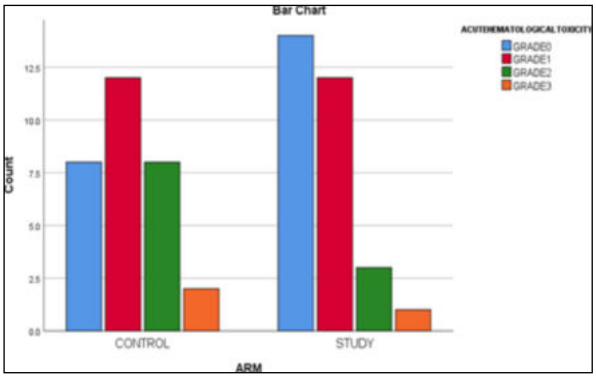


Figure -2. Comparison Of Haematological Toxicity Between The Arms

Grade 1(56.66% vs 40%) and Grade 2(16.66%vs10%) acute lung toxicity was numerically higher in study arm containing paclitaxel and carboplatin as concurrent chemotherapy but the difference is statistically insignificant (p value=0.153).

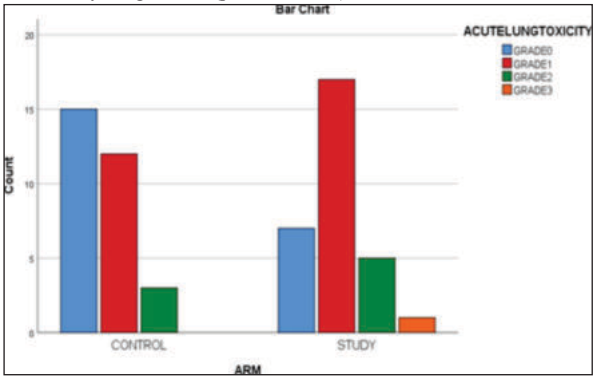


Figure -3. Comparison Of Acute Lung Toxicity Between The Arms

No statistically significant differences were found in terms of other toxicities like Acute esophageal (p-value 0.203) and skin toxicity (p-value 0.959) between the arms of the study.

DISCUSSION

Therapeutic approach in unresectable locally advanced non-metastatic non-small-cell lung cancer is widely discussed and a debatable one. External beam radiotherapy with concomitant chemotherapy is an acceptable approach for treatment in these cases. Concurrent

chemoradiotherapy has therapeautic advantages of reducing tumor volume, enhancing local control, treating micrometastatic disease and tolerability.Regarding the choice of chemotherapy regimen there are two major options – one is paclitaxel and carboplatin, another one is etoposide with cisplatin.

In this study 85% of patients were male with mean age of diagnosis 53.80 years in study Arm and 56.23 years in control Arm. Among them 83.3% patients were smoker. This data is corroborative with worldwide incidence of lung cancer in smoker.[7]

Adenocarcinoma (56.6%) followed by squamous cell carcinoma (35%) was the most common type of histology. Rising trend of adenocarcinoma in last 30 years is reflected in this study also[8].

In an attempt to improve the prognosis, concurrent chemoradiation was introduced and chemotherapy acts 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[9]. This study is an attempt to report our experience with concurrent chemoradiotherapy with paclitaxel and carboplatin (in study arm) versus concurrent chemoradiotherapy with cisplatin and etoposide (in control arm) in the treatment of locally advanced non-small cell lung cancer.

Wang et al. conducted a phase II randomized study of Cisplatin Etoposide (Cisplatin 50mg/m^2 on days 1,8,29,36 and Etoposide 50mg/m^2 on days1-5 and 29-33) versus weekly carboplatin (AUC = 2) and paclitaxel (45mg/m^2), both given concurrently with 60 Gy of thoracic radiation to patients with unresectable stage III NSCLC.[10] They found no significant differences between the regime in terms of overall response rate (ORR) and progression free survival(PFS) but higher neutropenia with Cisplatin- Etoposide.

Subsequently, a large, retrospective Veterans Administration– based study[11] comparing outcomes for Cisplatin-Etoposide versus Carboplatin- Paclitaxel given concurrently with radiotherapy was published and demonstrated no survival advantage for either regimen in a Cox proportional hazards model (hazard ratio , 0.97), although Carboplatin-Paclitaxel was better tolerated.

In our study also overall response rate (ORR) was not significantly different between the both arm .In our study overall response rate was 73% in concurrent chemoradiotherapy with paclitaxel and carboplatin and 70% in concurrent chemoradio-therapy with cisplatin-etoposide.

But, radiation pneumonitis is a concern with Paclitaxel-Carboplatin based concurrent chemo-radiation (CTRT).A multi-centric phase III trial reported by Liang et al.[12] compared two arms of concurrent Etoposide 50 mg/m^2 on days 1–5 and Cisplatin 50mg/m^2 on days 1 and 8 every 4 weeks for two cycles (EP) or paclitaxel 45mg/m^2 and carboplatin (AUC 2) on day 1 weekly (PC) along with 60–66 Gy of thoracic radiation therapy in each arm and found radiation pneumonitis more in PC arm whereas radiation esophagitis more in EP arm.

A systematic review of comparison of Conc. CTRT with either Cisplatin-Etoposide or Carboplatin-Paclitaxel in Stage III NSCLC revealed no significant difference in response rate, median PFS and Overall survival[13]. Cisplatin-Etoposide was associated with higher grade 3-4 haematological toxic effects.

In our study acute lung toxicity was numerically higher (p-value 0.153) with paclitaxel and carboplatin based regimen(study arm) and acute haematological (p-value 0.236) and esophageal toxicity was higher (p-value 0.203) in etoposide-carboplatin arm(control arm) although these differences are not statistically significant.

But,this study also has its limitations First,our sample size is small, so any statistical data have to be interpreted with caution. Secondly, it was a single institutional study; hence results derived cannot be extrapolated on entire population. Moreover, period of the study was short ,so the late toxicity profile , Disease free survival (DFS)/ Progression free survival (PFS) can't be assessed appropriately.

CONCLUSION

To conclude, there was no significant difference between concurrent chemo- radiotherapy with cisplatin and etoposide versus paclitaxel and carboplatin in locally advanced non small cell lung carcinoma in terms of local control and acute toxicity.. Further studies with larger sample size and longer duration of follow-up is necessary for defining an ideal concurrent chemotherapeutic regimen.

REFERENCES

1. Sung H,Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A,Bray F. Global Cancer Statistics 2020:GLOBOCAN Estimates of incidence and Mortality Worldwide for 36 cancers in 185 countries.CA Cancer J Clin. 2021 May;71(3):209-249.
2. Chapter 69: John DM. Neoplasm of lung. In: Anthony S. Fauci, Eugene Braunwald, K.J. Isselbacher, J.D. Wilson, J.B. Martin, D. L. Kasper, S.L. Hauser, D.L. Longo, editors, Principals of Internal Medicine. 14th ed. Mcgraw-Hill: 1998. P. 552-61.
3. Downey RJ, Martin N, Rusch VW. Extent of chest wall invasion and survival in patients of lung cancer. Ann Thorac Surg 1996;68:188-202.
4. Aupérin A, Le Péchoux C, Rolland E, et al. Meta-analysis of concomitant versus sequential radiochemotherapy in locally advanced non-small-cell lung cancer. J Clin Oncol. 2010;28n(13):2181-2190.
5. Non small Cell Lung Cancer Collaborative Group. Chemotherapy in non small cell lung cancer: A meta analysis using updated data on individual patients from 52 randomised clinical trials. BMJ 1995;311:899- 909.
6. Auperin A, Le Pechoux C, Pignon JP et al. On behalf of the Meta Analysis of cisplatin/carboplatin based Concomitant Chemotherapy in non small cell Lung Cancer (MAC3LC) Group. Concomitant radiochemotherapy based on platin compounds in patients with locally advanced non small cell lung cancer (NSCLC): A meta analysis of individual data from 1764 patients. Ann Oncol 2006;17:473- 83.
7. Thun MJ. Delancey JO ,Center MM, Jemal A, Ward EM. Theglobal burden of cancer: priorities for prevention. Carcinogenesis 2010;31(1):100.
8. Valaitis J, Warren S ,Gambel D. Increasing incidence of adenocarcinoma of the lung.Cancer 1981;47:1042.
9. Lawrence TS Blackstock AW, McGinn C. The mechanism of action radiosensitization of conventional chemotherapeutic agents. Semin Radiat Oncol 2003;13: 13-21.
10. Wang L , Wu S , Ou G et al. . Randomized phase II study of concurrent cisplatin/etoposide or paclitaxel/carboplatin and thoracic radiotherapy in patients with stage III non-small cell lung cancer . Lung Cancer 2012 ; 77:89 –96.
11. Santana-Davila R, Devisetty K, Szabo A, et al. Cisplatin and etoposide versus carboplatin and paclitaxel with concurrent radiotherapy for stage III non-small-cell lung cancer: an analysis of Veterans Health Administration data. J Clin Oncol. 2015;33 (6):567- 574
12. Liang J, Bi N, Wu S et al. Etoposide and cisplatin versus paclitaxel and carboplatin with concurrent thoracic radiotherapy in unresectable stage III non-small cell lung cancer: a multicenter randomized phase III trial. Ann Oncol. 2017 Apr 1;28(4):777-783.
13. Steuer E. Conor, Behera M, Ernani V et al. Comparison of Concurrent Use of Thoracic Radiation With Either Carboplatin-Paclitaxel or Cisplatin-Etoposide for PatientsWith Stage III Non–Small-Cell Lung Cancer: A Systematic Review. JAMA Oncol. 2017 Aug 1;3(8):1120-1129.