ORIGINAL RESEARCH PAPER
Volume - 13 | Issue - 05 | May - 2024 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

A COMPARATIVE STUDY ON TREATMENT RESPONSE AND TOXICITY BETWEEN SEQUENTIAL CHEMO-RADIATION THERAPY AND RADIATION THERAPY ALONE IN THE ELDERLY PATIENTS WITH INOPERABLE NON SMALL CELL LUNG CANCER

Radiotherapy

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ABSTRACT

Background: Lung cancer is one of the most common cancer and burden of cancer related deaths. Globally, it accounts for 11.6% of all new cancer cases and 18.4% of cancer related deaths. Many patients diagnosed with lung cancer are elderly, with a median age at diagnosis of 71 years. The study was taken up to evaluate the treatment response, toxicities, progression free survival and over-all survival in elderly patients with inoperable NSCLC treated with sequential chemoradiation therapy(SCRT) using intravenous Carboplatin and Gemcitabine combination chemotherapy versus radiation therapy alone. **Methodology:** This study was a randomized control trial, completed during the period of 1st November 2020 to 31st October 2022 in the department of Radiation Oncology, RIMS, Imphal where 96 patients who were histopathologically confirmed NSCLC cases were enrolled for the study. **Results:** In the control arm(radiation therapy alone), no patient achieved complete response compared to 6 patients (15%) in study arm. Partial response was found in 10 patients (25.6%) in control arm and 14 patients (35%) in study arm. There is significant benefit in achieving early treatment response among patients in study group (p=0.039). Progression free survival was longer among patients in study arm compared to control arm. **Conclusion:** Patients treated with SCRT was associated with increased treatment response and Progression free survival rate with increased acute manageable toxicities and comparable late side effects which were comparable to standard studies. Longer follow up with bigger sample size may be needed for drawing further conclusion.

KEYWORDS

Non Small Cell Lung Cancer, Sequential Chemoradiation, Gemcitabine, Carboplatin

INTRODUCTION:

Lung cancer is one of the most common cancer and burden of cancer related deaths all over the world. Globally, it accounts for 11.6% of all new cancer cases and 18.4% of cancer related deaths.[1]

Globally, the prevalant age of lung cancer is between the ages of 50-69, and only a small percentage (2%) of cancer had been reported under the age of 40 years.[2]The combination of radio- and chemotherapy have been recommended by guidelines for treating locally advanced disease.[3] Many patients diagnosed with lung cancer are elderly, with a median age at diagnosis of 71 years.[4] In India, lung cancer constitutes 5.9% of all new cancer cases and 8.1% of all cancer related deaths in both sexes.[5] Non-small cell lung cancer (NSCLC) histological subtype accounts for about 80% of the total lung carcinomas and the remaining 20% comprise of Small cell lung cancer (SCLC). NSCLC is a term used for a group of cancers originating in the lung that includes adenocarcinoma (30%-40%), squamous cell carcinoma (30%), undifferentiated large cell carcinoma (10%) and adeno-squamous carcinoma.[6] Non-small cell lung cancer is staged according to TNM staging based on tumour size, involvement of regional lymph nodes and whether it has spread outside the lung and/or to other parts of the body. Stage-I and II NSCLC are early stage NSCLC, stage-III is loco-regionally advanced lung cancer and stage-IV is metastatic NSCLC.[7]A number of studies have demonstrated that chemotherapy and radiotherapy can prolong survival and are recommended as treatment for locally advanced disease.[8] The combination of radiotherapy plus platinum-based chemotherapy for locally advanced NSCLC shows survival benefit compared with radiation therapy alone, and is considered the current standard of care.[9] The combination of radio- and chemotherapy have been recommended by guidelines for treating locally advanced disease.[10] The idea is that chemotherapy will reduce the risk of distant metastasis and radiotherapy will maintain loco-regional control.[11] Elderly patients with advanced NSCLC are usually not eligible for aggressive cisplatin-based chemotherapy because of the age-related reduction of the functional reserve of many organs and co-morbidities. Retrospective subgroup analyses of studies[12,13] suggested that Gemcitabine is effective with mild toxicity in the elderly lung cancer patients. The exact role of platinum compounds and combination chemotherapy for elderly patient is still being debated. Platinum combination chemotherapy is considered as a standard therapy for patients with NSCLC. However, very often there is hesitation of oncologists to add Cisplatin to treat elderly patients because of the concern about excessive toxicities and Carboplatin is less toxic than Cisplatin and it has been demonstrated to be just as efficacious for the treatment of NSCLC.[14]

A previous report suggested that intravenous Gemcitabine and Carboplatin combination as palliative chemotherapy in locally advanced NSCLC or metastatic NSCLC may be superior to Gemcitabine single therapy in terms of the response rate and overall survival and comparable non-hematologic toxicities.[15] Chemoradiation therapy is defined as treatment that combines chemotherapy with radiation therapy (RT). The methods of combining these two modalities are concurrent chemoradiation therapy (CCRT), defined as chemotherapy delivered within 30 days before or after initiation of RT, and sequential chemoradiation therapy (SCRT), defined as RT delivered more than 30 days after initiation of chemotherapy.[16] Sequential chemoradiotherapy proved to be superior to radiotherapy alone in the general population.[17,18] Even though specific data regarding advantage of sequential treatment in elderly patients are lacking, this approach is better tolerated than concurrent chemoradiotherapy (CCRT).[19,20,21]

Despite NSCLC constitutes between 80% and 85% of all lung cancers, and more than 30% of them are diagnosed with stage-III disease over the age of 65years, elderly patients are often excluded or underrepresented in the clinical trials of chemoradiation therapy resulting in limited treatment options for this population of patients[22,23]

Moreover,stage III NSCLC patients are typically elderly with co-morbidities, a group poorly represented in clinical trials, which may influence the choice for CCRT. Unfortunately, so far, no standard treatment modality has been established for elderly patients with inoperable NSCLC. Recently a retrospective study had shown that in elderly patients who received SCRT resulted in better overall survival than in those who received CCRT or radiation alone.[24]

In view of the available conflicting and limited data of benefits of SCRT in the elderly lung cancer patients, the study was taken up to evaluate the treatment response, toxicities, progression free survival and over-all survival in elderly patients with inoperable NSCLC treated with SCRT using intravenous Carboplatin and Gemcitabine combination chemotherapy versus radiation therapy alone.

MATERIALS AND METHODS:

This study was a randomized control trial, completed during the period of 1st November 2020 to 31st October 2022 in the department of Radiation Oncology, RIMS, Imphal Patients who are histopathologically confirmed inoperable NSCLC (Stage IIIA and IIIB) who reported to the Department of Radiation Oncology & Department of Respiratory Medicine RIMS, Imphal during the study period were enrolled. The Inclusion criteria are aged 60 years or older at the time of diagnosis**,** Karnofsky performance status (KPS) ≥ 60% and stage IIIA and IIIB Non-Small Cell Lung Cancer (NSCLC). Patients were allocated into Arm-A(Control-arm) and Arm-B(Interventional-arm) using simple randomisation method (Flipping a coin) where the side of the coin (i.e., heads – control-arm, tails – interventional-arm) determines the assignment of each participant. Age (in completed Years), Sex (Male/Female/Third gender), Stage (TNM Staging, AJCC 8th Edition), Histopathological type and Karnofsky performance status (KPS) wete the independent variables of the study. The dependent variables were early treatment response, early treatment toxicity, late treatment toxicity, progression-free survival and over-all survival. All the patients were subjected for complete history, thorough general physical examination, KPS score, complete blood count, blood chemistry, ECG, urine routine examination, blood sugar, chest X-ray (PA and lateral view), ultrasound whole abdomen, CT scan of Thorax and other investigations as per requirement. In Control-arm(Arm-A), patients had been treated with external beam radiation therapy using source axis distance (SAD) technique. The patients were treated with a total dose of 59.4Gy in 33 fractions by conventional fractionation (5 days in a week) over a period of 6-7 weeks.

In Interventional-arm(Arm-B), Patients had been treated with combination chemotherapy using intravenous Gemcitabine 1g/m^2 on Day 1 and Day 8 and Carboplatin 5AUC on Day 1 every 3 weekly for 2 cycles followed by the same radiation schedule and dosage as in the Arm-A after a gap of 2-3 weeks from the completion of 2nd cycle of Chemotherapy (after recovery from chemotherapy induced bone marrow suppression).Tumour volume definition for radiation therapy were based on the pre-chemotherapy tumour volume images. Carboplatin dosing was based on the area under the curve (AUC) method.

Dose(mg) = Target AUC × (CrCl +25), CrCl being the creatinine clearance.

Creatinine clearance = (140- Age) × mass(kgs) × 0.85(if female)/72 × serum creatinine(mg/dl)

Patients underwent check-up once in a week to evaluate the untoward side effects. Patients were subjected to weekly complete blood count and biochemical parameters (LFT, KFT) every 2 weeks. Treatment had been deferred if Hb%<10gm%, TLC<4000/cu-mm and platelet<1 lakh/cu-mm.

The early treatment response was assessed at 1 month after completion of treatment and late treatment response was assessed at the end of the study.

Early toxicities were assessed weekly from the 1st day of starting treatment till 2nd week after completion of treatment. Late toxicities were assessed after 3months from the completion of treatment for a minimum period of 6 months.

Treatment toxicity was assessed by Radiation Therapy Oncology Group (RTOG) Criteria Tumour response (both primary and nodal response) was assessed by WHO Response Criteria clinically and radiologically.

Statistical Analysis:

Descriptive data like age and median survival time were presented in terms of mean and standard deviation, data like sex, stage, performance status and toxicity profile were presented in terms of percentages and proportions, comparision of treatment response and toxicity profile between the two arms were analyzed using chi square test, for comparision of progression free survival, Kaplan meier survival curves with log rank test survival analysis were used, percentages, proportions and statistical significance were analysed using IBM SPSS statistics 26 for windows (IBM Corp, 1995, 2012), P value of < 0.05 was considered as significant.

Ethical Approval:

The permission of the Research Ethics Board, RIMS, Imphal, Manipur was obtained to conduct the study. Written informed consent of the patient were taken and registration were done before starting the study.

RESULTS:

In this study, a total of 96 patients were accrued , 48 patients in each arm. 5 patients lost to follow up and 4 patients drop out of treatment in study arm. Thereby only 39 cases in control arm and 40 patients in study arm were evaluable. In both the arms, maximum patients belong to the age group of 60-70 years, the median age in the control arm being 68 years and 69 years in the study arm. Out of 48 patients in each arm, number of male patients were 32 (66.7%) & 34 (70.8%) in the control & study arm respectively. 16 females (33.3%) &14 females (29.2%) were in the control arm and in the study arm respectively. Majority of patients presented with KPS of 70%; 52% & 56.3% in the control arm and study arm respectively. Table 1 shows tumor characteristics of the patients . Squamous cell carcinoma was the predominant histology types in the control arm(62.5%) and study arm(64.6%). Stage distribution among patients were comparable bwtween the two arms.

Table 1: Tumor Characteristics

Characteristics	Control Arm (N=48)	Study Arm (N=48)	P value
Histopathology			
Squamous	30(62.5%)	31(64.6%)	P=0.557
Adenocarcinoma	12(25.0%)	14(29.2%)	
Others	06(12.5%)	03(6.3%)	
Primary Tumor Status			
T1	01(2.1%)	04(8.3%)	P=0.572
T2	06(12.5%)	05(10.4%)	
T3	19(39.6%)	17(35.4%)	
T4	22(45.8%)	22(45.8%)	
Nodal status			
N0	06(12.5%)	05(10.4%)	P=0.812
N1	12(25.0%)	10(20.8%)	
N2	30(62.5%)	33(68.8%)	
Stage			
III-A	25(52.1%)	24(50.0%)	P=0.838
III-B	23(47.9%)	24(50.0%)	

Table-2, shows early treatment response, which were assessed as per WHO Miller's criteria, 1 month from the end of treatment completion. 6 patients (15%) in study arm as compared to none in control arm had complete response. 14 patients (35%) in study arm had partial response as compared to 10patients (25.6%) in control arm. The differences seen in between the arms were statistically significant (p=0.039). Stable disease was seen in 53.8% of patients in control arm and 37.5% of patients in study arm. 20.5% from control arm and 12.5% from study arm showed progressive disease.

Table 2: Early Treatment Response (Primary Site) (After One Month of Treatment Completion)

Type Of Response	Control Arm(A) (N=39)	Study Arm(B) (N=40)	P-Value
	No.(%)	No.(%)	
CR	0(0%)	06(15.0%)	P=0.039
PR	10(25.6%)	14(35%)	
SD	21(53.8%)	37.5%)	
PD	08(20.5%)	05(12.5%)	

Table-3 shows acute toxicities. Patients were assessed every week and maximum grade is noted. Anaemia & leucopenia were more observed in study arm as compared to control arm. Likewise, thrombocytopenia was also seen more in study arm than in control arm. Grade-3 thrombocytopenia was observed in 12.5 % of patients in study arm and 5.1% in control arm. Thus, overall haematological toxicities were more observed in study arm compared with control arm which were statistically significant. Increased grade 3 esophagitis was observed in study arm than in control arm (5% vs 2.5%). Grade1 nausea/vomiting were observed more common in study arm than in control arm (20% vs 10.2%). Grade 2 nephrotoxicity was observed more in study arm than in control arm (10% vs 2.5%)

Grade 1,2 and 3 pneumonitis were more in control arm than in study arm. The overall non-haematological toxicities in the study arm and control arm were comparable and shown statistically insignificant.

Table 3: Early treatment toxicity (Haematological Toxicity)

Haematological Toxicity	Control Arm (N=39)	Study Arm (N=40)	P-value
Anaemia			P=0.037
Grade 1	08(20.5%)	11(27.5%)	
Grade 2	05(13%)	14(35%)	
Grade 3	0	01(2.5%)	
Grade 4	0	01(2.5%)	
Leucopenia			P=0.035
Grade 1	12(30.7%)	03(7.5%)	
Grade 2	07(17.9%)	11(27.5%)	
Grade 3	0	03(7.5%)	
Grade 4	0	01(2.5%)	
Thrombocytopenia			P=0.003
Grade1	02(5.1%)	07(17.5%)	
Grade 2	02(5.1%)	10(25.0%)	
Grade 3	02(5.1%)	05(12.5%)	
Grade 4	0	0	

Table-4A, shows survival status of the patients at the end of study period. In control arm, 20 patients (51.3%) were progression free survivors whereas in study arm, 25 patients (62.5%) were progression free survivors. The median follow -up duration was 9 months for control arm and 12 months for study arm. Table -9B shows Difference in PFS in between the two arms is found to be statistically significant (p-value = 0.012).

Table-4A: Survival status of the patients

Type Of Response	Control Arm (N=39)	Study Arm (N-40)
PFS	20(51.3%)	25(62.5%)
OS	34(87.1%)	36(90%)
DEATH	05(12.8%)	04(10.0%)

Table-4B: Median Progression free Survival duration

	Control Arm	tudy Arm	P- Value
Number of patients	39	40	
Median progression free survival (PFS)	7 months	12 months	0.012*

*Log rank test

Figure 1: Kaplan Meire Survival Curve showing duration of progression free survival of the patients between the two arms.

As shown in figure-1, the median PFS was 12 months for the study arm and 7 months for the control arm. A total number of 9 patients had expired, 5 patients in control arm and 4 patients in the study arm.

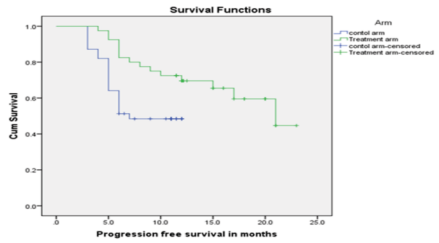

Figure 1: Kaplan Meire Survival Curve showing duration of progression free survival of the patients between the two arms.

Table-5, shows late treatment toxicity in both control and study arm. Patients were followed up every 3 months to assess the late side effects starting after 3 Months of treatment completion. Dysphagia was seen in one patient after 3rd month, one patient after 6th month and two patients after 9th month of treatment completion of evaluable patients in control arm. One patient after 3rd month, two patients after 6th month and three patients after 9th month developed dysphagia in study arm. Two patients in control arm and one patient in study arm developed stricture after 6th month of treatment completion. One patient in both control and study arm had myelitis after 6th month of treatment completion. One patient in each arm also had cardiac completion after 3rd month of treatment completion.

Table-5: Late treatment toxicity

Toxicity	Control arm			Study arm		
	M3	M6	M9	M3	M6	M9
Dysphagia	1(2.5%)	1(2.5%)	2 (5.1%)	1 (2.5%)	2 (5.0%)	3 (7.5%)
stricture	-	2(5.1%)	-	-	1 (2.5%)	-
Myelitis	-	1(2.5%)	-	-	1 (2.5%)	-
Cardiotoxicity	1(2.5%)	-	-	1 (2.5%)	-	-
Nephrotoxicity	-	-	-	-	-	-
Ototoxicity	-	-	-	-	-	-

(Assessed 3 monthly starting after 3 Months of treatment completion)

M3=assessment after 3rd month of treatment completion
M6=assessment after 6th month of treatment completion
M9=assessment after 9th month of treatment completion

DISCUSSION:

Treatment Response:

In terms of early response, there is significant benefit in achieving early treatment response (CR plus PR) in study group (p value=0.037). Percentage difference of PR (9.4%) in between the two arms in the present study was comparable to the finding by Dillmann et al where they observed a percentage difference of 8% in partial response between the sequential chemoradiation and radiation alone arm. A study by Pieree et al also shown response rate of 54% (CR plus PR) in sequential chemoradiation arm which was almost similar to our study findings where we observed overall(CR plus PR) response rate of 50% in study arm. In terms of late response, the median progression free survival (PFS) was 7 months for the patients in control arm and 12 months for the patients in study arm. Survival curve analysis showed statistically significant difference of PFS (p value=0.012) in between the two arms supporting sequentially chemo radiation compared with radiation therapy alone. Finding in our study is comparable to a study by Maguire et al where they found that the median progression free survival was 12.1 months in patients receiving sequential chemoradiation. Similarly, Davidoff et al also found that sequential chemoradiation has a significant survival benefit compared to radiation therapy alone (12.0 verses 7.6 months).

Toxicity Profile:

Similar hematological toxicities were observed in a study by Atagi et al where they observed more hematology toxicity in chemoradiation arm as compared to radiotherapy alone arm. In the present study, increased number of patients with increased haematological toxicities were observed but the toxicities were manageable similar to the study findings of Roy et al and Walter et al.Among the non-hematological toxicity, 41 % of patients had Grade 1 esophagitis in control arm as compared to 45% of patients in study arm. Findings of Grade 1 esophagitis in study and control arm are supported by study findings of Atagi et al where 46% patients in SCRT and 45 % in radiation arm had Grade 1 esophagitis. There was no statistical difference in number of pneumonitis cases between the two arms (p=0.152), which was supported by a study of Dawe et al. Comparison of number of patients with late toxicities between the two arms did not show any statistical significance which was similar to a study findings of Atagi et al Similar to the present study Roy et al observed more patients with late esophageal toxicity in 15% of patients receiving sequential chemoradiation.

CONCLUSION:

In the present study, it was found that there was statistically significant improvement in the early treatment response in study arm compared with control arm. Progression free survival was more in study arm as compared to control arm. Significant increase in acute treatment haematological toxicity were seen more in study arm than in control arm. Late side effects (dysphagia, myelitis, stricture) in both arms were comparable.

Thus, in the present study patients treated with sequential chemoradiation was associated with increased treatment response and Progression free survival rate with increased acute manageable toxicities and comparable late side effects.

Small sample size, conventional 2D planning and short follow up were the limitation of the present study. Therefore, longer follow up with bigger sample size may be needed for drawing further conclusion.

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