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OBSERVATIONAL STUDY OF RESPONSE AND TOXICITY OF CONCURRENT CHEMO RADIOTHERAPY FOLLOWED BY CONSOLIDATION CHEMOTHERAPY IN LOCALLY ADVANCED NON-SMALL CELL LUNG CARCINOMA

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ABSTRACT For Non-Small Cell Lung Cancer (NSCLC) simultaneous administration of radiotherapy with chemotherapy (concurrent or concomitant chemoradiation) followed by further chemotherapy (consolidation chemotherapy) has been shown to have better results compared to chemotherapy or radiotherapy alone. This study analysed the efficacy and effects of the same in Stage III NSCLC cases. 30 patients with proven stage III NSCLC who met the inclusion criteria were treated with 6 MV LINAC with MLC (3DCRT Planning). At the completion of concurrent treatment, 15% were CR and 59% were PR. At 3 months of follow-up, a total of nearly 70% patients responded to the treatment. The adverse effects studied included Esophagitis, Pneumonitis, Neutropenia, Thrombocytopenia and Leukopenia for a 3 month follow up period. The results obtained in our study support the observation that concurrent/consolidation chemoradiation with platinum containing regimens are superior to radiotherapy alone in terms of overall survival, disease-free survival and local control.

KEYWORDS : Concurrent Chemoradiation, Radiotherapy, Consolidation Chemotherapy, Non-smallcell Lung Cancer

INTRODUCTION

Worldwide, lung cancer is the most common cancer in terms of both incidence and mortality.[1,2] With increased smoking in developing countries, the rates are expected to increase. In India, about 63,000 new lung cancer cases are reported each year[3,4].

Non-Small Cell Lung Cancer (NSCLC) constitutes 75-80% of all lung cancers. More than 70% of these are in Stages III and IV when diagnosed making curative surgery difficult. While Small cell lung carcinoma (SCLC) usually responds better to chemotherapy, NSCLC is treated with surgery in the early stages and in locally advanced (stage III) cases combined modality treatments are practiced. These range from concurrent chemoradiation, systemic chemotherapy and radiotherapy to residual disease, radiation therapy alone to sequential chemoradiation.

Concurrent chemoradiation can either be induction/concurrent, and/or concurrent/consolidation. Trials have shown that addition of induction chemotherapy to concurrent chemoradiotherapy added toxicity and provided no survival benefit and that concomitant chemoradiotherapy is superior to sequential chemoradiotherapy.

This study evaluated the response with concurrent/consolidation chemoradiation treatment in Stage III NSCLC. Acute toxicities associated with it (hematological, pneumonitis, esophagitis) were studied.

MATERIALS AND METHODS

This prospective observational study was conducted at Saroj Gupta Cancer Centre and Research Institute, Kolkata, from September, 2013 to August, 2014. 30 patients were enrolled in the study with the following as the Inclusion criteria:

1. Age >18 & < 80 years of either sex
2. ECOG score ≤ 2
3. Cytologically/histopathologically and radiologically proven Stage III NSCLC
4. No distant metastases
5. LVEF ≥60%
6. FEV1 ≥1.5 litre
7. DLCO>60%
8. Haemoglobin ≥10 g/dl
9. Neutrophil count o> 1500/mm3
10. Platelet count ≥ 100,000/mm3
11. BUN ≤ 25 mg/dl,
12. Serum Creatinine ≤1.5 mg/dl
13. Serum Bilirubin ≤1.5 mg/dl,
14. ALT, AST ≤ twice the upper limit

THE EXCLUSION CRITERIA:

1. Restless patient unsuitable for radiotherapy
2. Pregnant or breastfeeding women
3. H/O allergic reaction to iodinated contrast media
4. H/O Chemo or Radio therapy for any cause

Patients meeting the above criteria were recruited after obtaining informed consent. Complete pretreatment evaluation was done using a predesigned proforma and clinical examination.

All patients underwent the following investigations: Complete Heamogram, RFT, LFT, ECG, Blood Grouping, FNAC and/or biopsy from the primary, Chest X-ray, CECT chest, USG abdomen. All patients were staged according to AJCC TNM Staging Manual 2012.

RADIOTHERAPY PROTOCOL

ENERGY:

6 MV Linear Accelerator with MLC (3DCRT planning); Siemens Primus Linear Accelerator and ONCENTRA 4.3 were used.

DOSE PRESCRIPTION:

60Gy in 30 fractions (2 Gy/fraction/5 days/week) in 6 weeks

CHEMOTHERAPY PROTOCOL:

Weekly D6, D13, D20, D27, D34, D41

Paclitaxel (40mg/m^2) /Carboplatin (AUC 2) for 6 weeks with radiation, followed by two courses of Paclitaxel (200 mg/m^2 on day1)/Carboplatin (AUC 5 on day 1) cycles being 21 days apart as consolidation chemotherapy

FOLLOW-UP:

Heamogram and biochemical investigations was done weekly. Acute toxicities were assessed once weekly. All Patients completing the complete schedule of radiotherapy and receiving minimum 4 cycles of

chemotherapy were evaluated for response. At the completion of treatment both the primary and the node response were noted for assessment of overall response.

Patients were assessed at completion of concurrent treatment, at 3 weeks and 3 months after completion of treatment. RECIST 1.1 criteria was used for assessment of overall response, RTOG grading for Pneumonitis and Esophagitis and CTCAE Criteria 3.0 for Haematological toxicity.

RESULTS

Out of 30 patients enrolled in the study 3 patients defaulted the treatment protocol. A total of 27 patients were taken for final analysis.

All the patients were male. The demographic details, tumour stage status, addiction history and the tumour histology for all the patients are shown in Tables 1 and 2.

Table-1: Demographic and personal details

Age Group (in years)	Number (n=27)	%
45-54	1	3.7%
55-64	14	51.9%
65-74	12	44.4%
Mean age	**63 ± 5.5**	
Personal Habits	**Number**	**%**
Smoking	23	76.6%
Smoking + Alcohol	5	16.6%
No	2	6.7%

Table-2: HPE and Grading

Tumour Histology	Number	%
Adeno Ca.	11	40.7%
Squamous cell Ca.	14	51.9%
Adeno-Squamous Ca.	2	7.4%
Distribution of patients according to AJCC stage		
STAGE III A	11	40.7%
STAGE III B	16	59.3%

The response to treatment of all the patients at the end of the CTRT, after 3 weeks of completion of CTRT and after 3 months of follow up are shown in Table 3.

Table-3: Distribution of response to treatment

Response	End of CTRT		At 3 weeks after CTRT		At 3 months after treatment	
	No	%	No	%	No	%
CR	4	14.8%	3	12.0%	4	14.8%
PR	16	59.3%	15	60.0%	15	55.6%
SD	5	18.5%	6	24.0%	8	29.6%
PD	2	7.4%	1	4.0%	0	0.0%
Total	27	100.0%	25	100.0%	27	100.0%

The proportion of patients with PR was significantly higher for all the time intervals (Z=6.04; p=0.0001). In 14.8% cases CR was found at 3 months after completion of treatment. Also, no PD was found at 3 months.

The various toxicities studied i.e. esophagitis, neutropenia, pneumonitis, leukopenia and thrombocytopenia are shown in Tables 4, 5, 6, 7 and 8 respectively.

Table-4: Distribution of toxicity of oesophagus

Grade	Highest Grade Reaction during CTRT		At 3 weeks after completion of CTRT		At 6 weeks after completion of CTRT		At 3 months after treatment	
	No	%	No	%	No	%	No	%
Grade-0	0	0.0%	4	16.0%	13	50.0%	18	66.7%
Grade-1	5	18.5%	7	28.0%	8	30.8%	7	25.9%
Grade-2	15	55.6%	9	36.0%	4	15.4%	2	7.4%
Grade-3	7	25.9%	5	20.0%	1	3.8%	0	0.0%
Grade-4	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Grade-5	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Total	27	100.0%	25	100.0%	26	100.0%	27	100.0%

Toxicity of oesophagus significantly decreased over time and 3 months after completion of treatment proportion of patients with no toxicity (66.7%) was significantly higher (Z=5.78; p=0.0001).

Table-5: Distribution of toxicity in neutropenia

Grade	Highest Grade Reaction During CTRT		At 3 Weeks After CTRT		At 6 Weeks After CTRT		At 3 Months After Treatment	
	No	%	No	%	No	%	No	%
Grade-0	0	0.0%	3	12.0%	3	12.0%	24	88.9%
Grade-1	7	25.9%	6	24.0%	6	24.0%	3	11.1%
Grade-2	14	51.9%	12	48.0%	12	48.0%	0	0.0%
Grade-3	6	22.2%	4	16.0%	4	16.0%	0	0.0%
Grade-4	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Grade-5	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Total	27	100.0%	25	100.0%	26	100.0%	27	100.0%

Toxicity of Neutropenia significantly decreased over time and 3 months after completion of treatment proportion of patients with no toxicity (88.9%) was significantly higher (Z=11.00; p=0.000001).

Table-6: Distribution of pneumonitis

Grade	Highest Grade Reaction during CTRT		At 3 weeks after completion of CTRT		At 6 weeks after completion of CTRT		At 3 months after treatment	
	No	%	No	%	No	%	No	%
Grade-0	0	0.0%	6	24.0%	14	53.8%	19	70.4%
Grade-1	14	51.9%	10	40.0%	10	38.5%	8	29.6%
Grade-2	9	33.3%	6	24.0%	2	7.7%	0	0.0%
Grade-3	4	14.8%	3	12.0%	0	0.0%	0	0.0%
Grade-4	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Grade-5	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Total	27	100.0%	25	100.0%	26	100.0%	27	100.0%

Toxicity in lung significantly decreased over time intervals and 3 months after completion of treatment proportion of patients with no toxicity (70.4%) as significantly higher (Z=5.76; p=0.0001).

Table-7: Distribution of Leukopenia

Grade	Highest Grade Reaction during CTRT		At 3 weeks after CTRT		At 6 weeks after CTRT		At 3 months after treatment	
	No	%	No	%	No	%	No	%
Grade-0	0	0.0%	3	12.0%	8	30.8%	22	81.5%
Grade-1	5	18.5%	7	28.0%	11	42.3%	5	18.5%
Grade-2	10	37.0%	7	28.0%	4	15.4%	0	0.0%
Grade-3	12	44.4%	8	32.0%	3	11.5%	0	0.0%
Grade-4	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Grade-5	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Total	27	100.0%	25	100.0%	26	100.0%	27	100.0%

Toxicity of leukopenia significantly decreased over time and 3 months after completion of treatment proportion of patients with no toxicity (81.5%) was significantly higher (Z=8.91;=0.00001).

Table-8: Distribution of toxicity of Thrombocytopenia

Grade	Highest Grade Reaction during CTRT		At 3 weeks after completion of CTRT		At 6 weeks after completion of CTRT		At 3 months after treatment	
	No.	%	No.	%	No.	%	No.	%
Grade-0	0	0.0%	4	16.0%	4	15.4%	25	92.6%
Grade-1	15	55.6%	7	28.0%	14	53.8%	2	7.4%
Grade-2	8	29.6%	10	40.0%	6	23.1%	0	0.0%
Grade-3	4	14.8%	4	16.0%	2	7.7%	0	0.0%
Grade-4	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Grade-5	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Total	27	100.0%	25	100.0%	26	100.0%	27	100 %

Toxicity of thrombocytopenia significantly decreased over time intervals and 3 months after completion of treatment proportion of patients with no toxicity (92.6%) was significantly higher (Z=12.04;=0.000001).

DISCUSSION

In this study ~95% of patients were >57 years of age at presentation with median age of 64 years. This matches the expected age distribution of 5th - 7th decades as shown by Yamamoto et al[5]. and Belani et al[6]. Lung cancer is more common in males and this study reflected the same. Our study had 93% smokers and was in concordance with other studies.

In a study by Belani et al[6] 81% of the patients received planned radiotherapy dose, and 93% of patients received 5 or more cycles of chemotherapy during concurrent phase, and 75% of patients received 1 or more cycles of consolidation chemotherapy. In our study, 92.6% of patients completed the intended treatment protocol. The rate of

compliance was similar that reported by Yamamoto et al[5].

Concurrent administration of chemoradiotherapy is a promising approach for treating patients with locally advanced lung cancer. Moreover, chemotherapy given as a part of concurrent chemoradiation may act systematically and potentially eradicate distant micromet astases. Concurrent chemoradiation treatment with platinum con taining regimens has proven to be superior to radiotherapy alone in terms of overall survival, disease-free survival and local control as shown by NSCLC Collaborative Group Meta-analysis[7] and Le Chevalier et al[8].

At completion of treatment 15% had CR and 59% PR. Overall survival rates in consolidation arm were 63%, 31%, and 17% at 1, 2, and 3 years respectively. Our results are in conjunction with the results of studies in which concurrent chemotherapy was used. In a phase III trial by Yamamoto et al the objective response rate was 63.3% consolidation arm, 3- and 5-year survival rates 26.4%, and 19.5%.

In our study Grade 2-3 Esophagitis was reported during RT in 81.5% of patient population of which 26% had Grade 3 Esophagitis, which is comparable to the results reported by Belani et al who reported a 26% grade 3/4 toxicity in oesophagus during treatment while Yamamoto et al had the incidence of grade 2 or worse Esophagitis as 33.3%.

In our study, most of the patients had Grade1-2 acute toxicity of Pneumonitis. Belani et al reported 16% lung toxicity in their study and Yamamoto et al reported 4% lung related toxicity during the course of treatment. In our study Grade 3 acute toxicity developed in only 15% of patients during RT. At 3 months of follow-up, most patients had no significant respiratory symptoms.

In our study patients reported with Grade 3 neutropenia are 22% during RT. At 6 weeks 16% of patients had grade 3 toxicity and 48% had grade 2 toxicity. At 3 months of follow-up, 11% had grade 1 late toxicity. Yamamoto et al had the incidence of Grade 3 or Worse Neutropenia as 23.1% during Concurrent Phase and 61.9 % during the treatment and Belani et al had Grade 3/4 Granulocytopenia occurring in 26% of patients.

Patients with Grade 1-2 thrombocytopenia were more during RT and it increased during consolidation chemotherapy: at 3 weeks 16% had grade 3, 40% had grade 2 toxicity, and at 6 weeks 7% had grade 3 while 23% had grade 2 toxicity. At 3 months of follow up most patients had no thrombocytopenia, similar observations were seen by Yamamoto et al.

CONCLUSION

Concurrent administration of chemotherapy and radiotherapy is a promising approach for treating patients with locally advanced lung cancer. Moreover, chemotherapy given as a part of concurrent chemoradiation may act as chomosensitizer and potentially eradicate distant micrometastases. Concurrent chemoradiation treatment with platinum containing regimens has proven to be superior to radiotherapy alone in terms of overall survival, disease-free survival and local control.

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