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A PROSPECTIVE STUDY TO SEE THE FEASIBILITY, EFFICACY AND TOXICITY OF INDUCTION CHEMOTHERAPY FOLLOWED BY CHEMORADIATION IN STAGE III NON-SMALL CELL LUNG CANCER

[1,*]Dr. Pritam Kumar Sardar, [2]Dr. Lekshmi R. Shenoi and [3]Dr. Sumana Maiti

[1]Clinical tutor, Department of Radiotherapy, Malda Medical College, Malda -732101, India
[2]Post Graduate Trainee, Department of Radiotherapy, Institute of Post graduate Medical Education and Research, Kolkata -700020, India
[3]Assistant Professor, Department of Radiotherapy, Institute of Post graduate Medical Education and Research, Kolkata -700020, India

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***Corresponding author:* Dr. Pritamkumar Sardar**

ABSTRACT

Purpose: This study was designed to observe the epidemiology, acute toxicities, overall survival at one year, disease free survival (DFS) and progression free survival (PFS) for stage III non-small cell lung cancer. ***Materials and methods:*** After undergoing pretreatment assessment with history, physical examination and baseline laboratory investigations and imaging, eligible patients were treated with two cycles of induction chemotherapy consisting of injections Paclitaxel, Carboplatin followed by concurrent chemoradiotherapy with weekly injections Paclitaxel, Carboplatin and 66 Gy radiation. Evaluation was done weekly during treatment, at 6th weeks after completion of treatment and thereafter 3 monthly till the end of study. ***Results****:* Among 42 patients, males (95.2%), smokers (85.7%) were predominant with squamous cell carcinoma (52.4%) as most common histology. Mean age of diagnosis was 55.1 years. Overall response rate (Complete Response + Partial Response) was 66.7% at one year. Acute toxicities were tolerable and managed conservatively. Mean DFS and PFS were 10 months and 11.8 months respectively. ***Conclusion:*** To conclude this study was feasible as the toxicities were limited and manageable. Most of the patients responded well. For further conclusion, large number of patients should be included and compared to a control arm.

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INTRODUCTION

Lung cancer is one of the leading cause of cancer mortality with a rate of increase of 0.5% per year throughout the world (Magrath and Litvak, 1993). 85% of all lung cancer are non-small cell lung cancer (NSCLC), of which squamous cell carcinoma is the major histologic variant followed by adenocarcinoma and large cell lung cancer. As most of the lung cancers present in late stage, they are potentially inoperable and chance of distant metastasis is very high (Perez and Brady, 2018). Patients with locally advanced NSCLC, the preferred treatment is platinum based chemotherapy administered concurrently with radiotherapy (Schaake-Koning *et al.,* 1992). Induction chemotherapy may improve systemic control and concurrent chemotherapy appears to increase loco-regional control. Several studies explored the administration of more intensive platinum doublet chemotherapy as induction chemotherapy and concurrently during radiotherapy, increase overall median survival time than previously achieved with induction (neoadjuvant) chemotherapy alone (Vokes *et al.,* 2002). Primary objective of the study was to assess the responses according to RECIST V1.1, in terms of Complete Response (CR), Partial Response (PR), Progressive Disease (PD) and Stable Disease (SD) and the Secondary Objectives were to study the acute toxicities with the help of RTOG radiation morbidity criteria (CTC V1.1) and to assess overall survival of one year, DFS (for complete responders) and PFS (for partial responders and stable disease).

MATERIALS AND METHODS

Before the inception of the study an application was submitted to the institutional ethics committee (IEC). IEC after proper scrutiny and detailed review, approved the research proposal. This was a prospective, interventional study in a tertiary care

hospital. After confirmation of diagnosis by CT guided core needle biopsy, newly diagnosed 42 non metastatic non -small cell lung cancer patients aged 18 to 70 years, having good performance status (ECOG 0-2), without any severe systemic co-morbidities or uncontrolled severe haematological abnormalities with inoperable stage IIIA & IIIB disease [T1N2, T2N2, T3N1, T3N2, T4N0, T4N1 (Stage IIIA) & T1N3, T2N3, T3N3, T4N2, T4N3 (Stage IIIB)] were included in this study in the period of January 2016 to August 2017.Pregnant patients were excluded. Eligible 42 patients for study received two cycles of induction chemotherapy consisted of Paclitaxel 200mg/m^2 and Carboplatin (AUC-6) intravenously every 21 days prior to chemoradiotherapy. Concurrent chemoradiotherapy was given with a total dose of 66Gy radiation dose at 2Gy/fraction, single fraction per day, five fractions (from Monday to Friday) per week for 6 weeks 3 days and patients received weekly chemotherapy with injection Paclitaxel 50mg/m^2 and Carboplatin (AUC-2) intravenously on every Monday during treatment. Injection Paclitaxel is a M phase specific chemotherapeutic drug which acts by microtubule polymerisation. Injection Carboplatin is a non-cell cycle specific drug and acts by DNA adduct formation. Injection Paclitaxel was infused first in 500 ml normal saline bottle for 1hr (for concurrent chemotherapy) and 3 hours (for induction chemotherapy). Injection Carboplatin was infused in 500 ml D5 over 90 mins as second bottle. All patients received tab. Avil (pheniramine) 50mg, injection Dexamethasone 20 mg, injection Ondensetron 16 mg and injection Ranitidine 50 mg as premedication.

Radiation treatment was executed in bhabatron II (Cobalt -60) treatment unit with a planning software oncentra (version-4.5.3). While taking CT images patients were in supine position with both arms rested above the head and same were sent to Oncentra (version- 4.5.3) software for contouring and planning. The clinically macroscopic diseases typically identified on imaging was contoured as gross tumor volume (GTV & GTV node). The clinical target volume (CTV) represents a volumetric expansion of the GTV to encompass microscopic disease. For squamous cell carcinoma 6 mm expansions, for adenocarcinoma 8 mm expansions and for nodes less than 2 cm, 5 mm expansion was taken. The planning target volume (PTV), the volumetric expansion of the CTV to account for set-up variability was generated by giving a margin of 2 cm three dimensionally. Dose constraints for bilateral lungs excluding the PTV, oesophagus, heart, spinal cord were considered. According to QUANTEC data for lung, the dose constraint is V20 <30-35Gy (V20 is defined as the percentage of normal lung receiving at least 20 Gy and is dependent on the total lung volume) with conventional fractionation in dose volume histogram (DVH). For oesophagus, the collected data suggests that volumes treated at more than 40-50 Gy correlate to acute symptoms. For heart and pericardium the dose constraints of QUANTEC data reflects conservative interpretation of existing literature. If the V25 is less than 10%,then the excess risk of cardiac mortality attributable to ischemic changes is less than 1% at 15 yrs.The risk of pericarditis can be minimised by keeping V30<46%. For spinal cord the dose constraint is 45Gy using conventional (1.8 Gy) fractions. Generally for Phase I,AP-PA(A-anterior, P-posterior) fields were used to treat the patients. Multiple fields were also used such as 3 fields (AP and two lateral fields) if required. For Phase I the prescribed dose was 46 Gy in 23 fractions, 5 fractions/ week in 4.5 weeks and dose was prescribed at mid plane for AP-PA field. For Phase 2 generally 3 fields were used for better optimal dose distribution. The dose was 20 Gy in 10 fractions, 5 fractions/ week in 2 weeks. Dose to be prescribed at normalisation point on GTV. Patients were evaluated for acute toxicities each week on Monday during radiation therapy by physical examination and blood for complete blood count (CBC), serum urea (Ur), serum creatinine (Cr) and liver function tests (LFT). They were graded according to the RTOG Radiation Morbidity Criteria. For assessment of clinical response, in terms of complete response (CR), partial response (PR), progressive disease(PD), and stable disease(SD), RECIST (Response Evaluation Criteria in Solid Tumor) was used. Patients were assessed at 6 weeks after completion of treatment with CECT thorax, USG whole abdomen, blood for CBC, LFT, Ur, Cr. Thereafter every 12 weekly interval till the end of study by physical examination, digital chest X-ray PA view, blood for CBC, LFT, Ur, Cr were assessed. If there was any suspected lesion, CECT scan of that region was advised. Recurrence was proved with either biopsy or FNAC. In case of suspected brain metastasis, MRI gadolinium contrast of brain was advised. Statistical analysis was done using SPSS version 18 and MS excel software.

RESULTS

Among 42 patients, 40 patients were males (95.2%) and 2 were females. 36 of them were heavy smokers (85.7%) with a history of 18±5-pack-years of cigarette smoking. Most common histology was squamous cell carcinoma (52.4%) followed by adenocarcinoma (28.6%).Mean age of diagnosis was 55.1±2.8 years, ranging from 37 years to 63 years. The two female patients were non-smokers and diagnosed with adenocarcinoma. T3(47.6%) and N2 (38.1%) were predominant tumour and nodal stages respectively. In this study 20 patients showed CR(47.6%), 8 showed PR(19.1%), 8 had SD(19.1%), 6 had PD(14.3%). The 6 patients with progressive disease died during the study. So overall response rate (Complete Response + Partial Response) was 66.7%. Most common acutetoxicity was haematological toxicity (80.9%) but was tolerable and managed conservatively as most of them were grade 2(58.8%). Mean DFS was 10 months with standard error of 1.7 (95%confidence interval; lower bound 6.6 and upper bound 13.4). Mean PFS was 11.8 months with standard error of 1.3 (95%confidence interval; lower bound 9.2 and upper bound 14.4).

DISCUSSION

Lung cancer is one of the most common malignancies worldwide. In this study 95.2% of patients were males with mean age of diagnosis (55.1±2.8) years. Among them 85.7% patients were smokers. This data is corroborative with world incidence lung cancer in smokers (Thun *et al.,* 2010). Analysis of data from 22 cancer registries in 5 continents revealed that cumulative lung cancer risks were higher in males than in female (Sano *et al.,* 2006). Approximately 80% of non-small lung cancer (NSCLC) in men worldwide are directly attributable to cigarette smoking (Levin *et al.,* 1950). These features were encountered in our study population also. The patients were diagnosed by CT guided trucut biopsy or bronchoscopic biopsy. Squamous cell carcinomas (52.4%) followed by adenocarcinomas (28.6%) were the most common type of histologic types. Rising trend of adenocarcinoma in last 30 years was seen (Vokes *et al.,* 2007). The optimum treatment modality for unresectable non-small-cell lung cancer

is yet to be defined. Induction chemotherapy has several theoretical advantages, including reducing tumour volume, enhancing local control, treating micro-metastatic disease, and being better tolerated. There are few trials that have reported on the use of induction chemotherapy followed by chemo-radiotherapy. A CALGB trial randomised 366 patients with stage III NSCLC to immediate chemotherapy (Carboplatin, Paclitaxel) or induction chemotherapy with two cycles Carboplatin and Paclitaxel prior to chemo-radiotherapy showed that survival differences were not statistically significant with induction chemotherapy (12 months vs. 14 months, *p value -.0.3*).

The addition of induction chemotherapy to concurrent chemo-radiotherapy added grade 4 toxicity (24%vs.41%, *p value-0.001*) (Vokes *et al.,* 2007). In this study most of the cases were grade 2 toxicity. There was no grade 4 toxicity. Iranzo *et al.* did a study on induction chemotherapy followed by concurrent chemo-radiotherapy for patients with non-operable stage-III non-small-cell lung cancer observed that overall response rate was 64.6% with grade 3,4 haematological and grade 2 oesophagus toxicity (28.1% cases) (Iranzo *et al.,* 2009). A phase –II trial by Hirsh *et al.* with Carboplatin /Gemcitabine as induction chemotherapy followed by radiotherapy concomitantly with Paclitaxel /Gemcitabine in stage III NSCLC showed partial response (PR) was 74%, stable disease (SD) 24% and 2% had progressive disease(PD) with minimal toxicity (Hirsh, 2006).

In an attempt to improve the prognosis, concurrent chemoradiation was introduced and chemotherapy acts as a radiosensitizer when administered concurrently. The combination of chemotherapy and radiation may improve the local control and survival rate because of the additive or synergistic effect of chemo-radiation (Lawrence *et al.,* 2003). In this study overall response rate was 66.7% in induction chemotherapy arm and Iranzo *et al.* reported 64.6% overall response rate in a similar study. With a mean follow up of 7.5 months, mean DFS was 10 months with standard error of 1.7(95%confidence interval CI; lower bound 6.6 and upper bound 13.4).Mean PFS was 11.8 months with standard error of 1.3(95%CI; lower bound 9.2 and upper bound 14.4).Acute haematological toxicity (80.9%),acute lung toxicity(23.8%), acute pharynx and oesophagus toxicity (52.4%) and skin toxicity(38.1%) were very tolerated in this study. So, the study had satisfactory response rate with limited toxicities. Sample size in this study was small, so any statistical data has to be interpreted with caution. Being a single institutional study; results derived cannot be extrapolated on entire population. Usually this cancer recur within 24 months, more so in first twelve months post-treatment. Entire study duration was almost 1.5 years including patient accrual, intervention and assessment. So the toxicity profile or DFS/PFS may be changed with longer follow up. In analysis, contributing factors such anaemia, duration of treatment interruption, overall treatment time(OTT), deterioration of nutritional status with fall in quality of life (QOL) were not adjusted for assessing the response rate and DFS/PFS. As the duration of the study was small, analysis of chronic toxicity was not included in the study.

Conclusion

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