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A PROSPECTIVE INTERVENTIONAL STUDY COMPARING PALLIATIVE RADIOTHERAPY WITH AND WITHOUT CYCLOPHOSPHAMIDE IN METASTATIC NON-SMALL CELL LUNG CANCER

Radiotherapy

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ABSTRACT

Background: Management of Stage IV lung cancer is decided according to the patient's symptoms and general condition. Palliation can be achieved with external-beam RT for primary disease with localized symptoms. The purpose of this study is to compare the effect of palliative radiotherapy with and without cyclophosphamide in terms of symptomatic relief and quality of life in metastatic cases of non-small cell lung carcinoma. **Materials and Methods:** This prospective comparative study included 70 patients of metastatic non-small cell lung cancer with 35 cases in the study arm subjected to palliative radiotherapy with concurrent cyclophosphamide and 35 cases in the control arm receiving palliative radiotherapy alone. Patients were initially evaluated with history, clinical examination, blood investigations and imaging. All patients received radiotherapy to the primary site with a total dose of 30Gy in 10 fractions over 2 weeks. Patients in study arm received concurrent Tab Cyclophosphamide 50mg OD. All patients were assessed for symptomatic relief at 4 weeks after completion of treatment including cough, breathlessness, chest pain and hemoptysis. Quality of life using FACT-G questionnaire was assessed after 4 weeks of treatment completion. Response evaluation, hematological and skin toxicities were also evaluated. **Results:** In the study arm, 14 patients had >50% relief in cough, 12 patients had >50% relief in breathlessness and 9 patients had >50% relief in chest pain while in the control arm, 10 patients had >50% relief in cough, 10 patients had >50% relief in breathlessness and 7 patients had >50% relief in chest pain. Patients in both arms had complete relief in hemoptysis. The mean FACT-G scores post-treatment was 72.05 and 64.12 in the study arm and the control arm, respectively. Both the groups had comparable tumour response after treatment. **Conclusion:** An improved but not statistically significant ($p>0.05$) difference was observed in symptomatic relief as well as quality of life in patients in both the arms. Concurrent cyclophosphamide with radiotherapy may be a tolerable and cost-effective option in palliative treatment of metastatic non-small cell lung cancer but a larger sample size and better radiation technique is required for a solid inference.

KEYWORDS

Metastatic non-small cell lung cancer, palliative radiotherapy, cyclophosphamide, symptomatic relief, quality of life

INTRODUCTION

Lung cancer has been amongst the leading cancers for a number of years posing a serious public health concern. It is the most frequently diagnosed cancer worldwide with an estimated 2.4 million new cases (12.4%) and the leading cause of mortality with around 1.8 million deaths (18.7%) according to GLOBOCAN 2022. It is the second most common malignancy in males (8.5%) and fourth overall (5.8%) With an estimated incidence of 81,748 in 2022 in India, [1] Due to the disparity in the socioeconomic status and healthcare accessibility contributing to the delay in diagnosis and treatment, a major proportion of patients have locally advanced or metastatic lung cancer at initial presentation. Smoking is the most commonly associated risk factor. 80% of lung cancer patients report a significant smoking history. [2] The risk increases exponentially with increased number of packs smoked per day and the number of years smoked. Significant occupational exposure to asbestos, silica, arsenic and beryllium, indoor air pollution and personal or family history of lung cancer also serves as risk factors that determine its development. Broadly, Small cell lung cancer and Non-small cell lung cancer (NSCLC) are the two main types which constitute 15% and 85% of all the lung cancer cases respectively.[3] Squamous cell and large cell cancers are strongly associated with smoking whereas adenocarcinoma is the most prevalent lung cancer type in smokers as well as non-smokers, in both men and women, irrespective of age. Metastatic lung cancer is managed depending on the patient's symptoms and general condition. Main symptoms are cough, dyspnoea, chest pain, hoarseness, superior sulcus syndrome, superior vena cava syndrome, and haemoptysis. A multidisciplinary approach is required to provide the best supportive care as well as disease-directed and life-prolonging interventions. A balance between adequate symptom relief and possible toxicities of the treatment is important. This is achieved via early integration of palliative treatment, traditionally including palliative radiotherapy (PRT), palliative chemotherapy or both. Palliative radiation therapy (PRT) is a well-tolerated and time-saving intervention which plays a crucial role in preventing progression of disease, providing symptomatic relief as well as improving the quality of life. It is a potentially valuable modality in appropriately selected patients with metastatic disease. Systemic therapy is recommended for disseminated disease which depends on the histologic type, somatic genomic alterations that can be treated with targeted therapy, and performance status. Targeted therapy in metastatic NSCLC has been shown to decrease tumour burden and improve the quality of life for patients with specific variants. Cyclophosphamide is a chemotherapy drug, an alkylating agent that acts by inhibiting protein synthesis through DNA and RNA crosslinking. Low-dose cyclophosphamide may be a suitable and cost-effective drug as concurrent chemotherapy with palliative radiotherapy in metastatic non-small cell lung carcinoma.

MATERIALS AND METHODS

This was a prospective comparative study conducted on 70 patients of metastatic Non-small cell lung cancer reporting to the Department of Radiation Oncology at a tertiary care hospital.

The participants included in the study were patients with histopathologically proven Non-Small Cell Carcinoma Lung, age 18-70 years, Stage IV (AJCC 8th edition), KPS (Karnofsky Performance Scale) 40 to 70, patients fit to receive treatment with normal metabolic and hematological profile and patients willing to sign informed consent and be a part of this study. Patients with history of previous treatment with Surgery or Radiotherapy to thorax and any uncontrolled current illness, pregnant & lactating women, immunocompromised state were excluded from the study.

Initial Evaluation

This included history and physical examination, histopathological examination, routine blood examination and viral markers study, chest X-ray and USG abdomen, Contrast-enhanced computed tomography of thorax and whole abdomen and PET-CT scan for staging.

Methodology

Patients were randomly assigned to the study and control arms with 35

patients in each arm. Patients in the study arm received Palliative Radiotherapy with Cyclophosphamide and while in the control arm patients received Palliative Radiotherapy alone.

Radiotherapy
All patients were treated by external beam radiation using 2D technique on Cobalt-60 machine. Patients received Radiotherapy to the primary site with a total dose of 30Gy in 10 fractions at 3Gy per fraction over 2 weeks.

Chemotherapy
Patients in study arm were given concurrent Tablet Cyclophosphamide 50mg once daily before each fraction.

Evaluation During Treatment
Hematological and skin toxicities were assessed weekly during treatment using CTCAE (Common Terminology Criteria for Adverse Events) and RTOG Criteria (Radiation Therapy Oncology Group) respectively.

Evaluation at Treatment Completion
All patients were assessed for symptomatic relief at 4 weeks after completion of treatment, including Cough (using Visual Assessment Scale), Breathlessness (using MRC breathlessness scale), Chest pain (using Universal pain assessment tool) and Hemoptysis (using hemoptysis assessment). Hematological and skin toxicities were also scored at 4 weeks of completion of treatment. Response evaluation was done after 4 weeks of treatment completion by digital X-ray/CECT Chest using RECIST criteria version 1.1(Response Evaluation Criteria in Solid Tumors). All patients were assessed for quality of life using FACT-G questionnaire (Functional Assessment of Cancer Therapy-General) before the initiation of treatment and after 4 weeks of treatment completion.

Statistical Analysis
Continuous variables were summarized in form of mean and were analysed using unpaired t test. Nominal/ Categorical variables were summarized in form of proportions and analysed using Chi-Square/ Fisher exact test. p-value <0.05 was taken as significant.

RESULTS
70 patients of non-small cell lung cancer were included in this study of which 56 were males and 14 were females. These patients were randomly divided into two groups of 35 patients each. The mean age was 57.97 yrs in study arm and 60.34 yrs in control arm. The no. of patients with smoking history was 66 including both arms. Squamous cell carcinoma histology was 40% and 49% adenocarcinoma histology were 40% and 37% respectively in the study and control arms. Patients in study arm received Palliative Radiotherapy with Cyclophosphamide and while in control arm patients received Palliative Radiotherapy alone.

	ARM A (study arm)	ARM B (control arm)
No. of patients	35	35
Mean age (years)	57.97	60.34
Gender		
-males	27	29
-females	8	6
Smoking	32	34
Median KPS	60	50
Histology		
-Squamous cell ca	14	17
-Adenocarcinoma	14	13
-other	7	5

	ARM A (study arm)	ARM B (control arm)
	Before Treatment	Before Treatment
SYMPTOMS		
- Cough	24 (69%)	23 (66%)
- Breathlessness	24 (69%)	23 (66%)
- Chest Pain	20 (57%)	19 (54%)
- Hemoptysis	5 (14%)	4 (11%)

FACT G Score				
-Mean	63.44	72.05	59.58	64.12
-Median	62	73	58	65

Symptomatic Relief After 4 Weeks of Treatment Completion in Both the Arms
Cough: Patients were assessed at 4 weeks after treatment completion using visual assessment scale. In study arm, 14 patients had >50% relief in cough while in control arm, 10 patients had >50% relief. 25-50% relief in cough was seen in 6 patients in both study arm and control arm respectively.

Breathlessness: Patients assessed for breathlessness using MRC scale after 4 weeks of treatment completion. In study arm, 12 patients had >50% relief in breathlessness while in control arm, 10 patients had >50% relief. 25-50% relief in breathlessness was seen in 7 and 8 patients in study arm and control arm respectively.

Chest Pain: Universal Pain Assessment Tool was used for assessing chest pain. In study arm, 9 patients had >50% relief in chest pain while in control arm, 7 patients had >50% relief. 25-50% relief in chest pain was seen in 8 patients in both study arm and control arm respectively.

Hemoptysis: Out of the total of 9 patients with hemoptysis pre-treatment, 5 had complete relief after treatment in study arm and 4 in control arm.

	SUBJECTIVE RELIEF IN SYMPTOMS			
	>50%	25-50%	<25%	No Relief
Study arm				
-cough	14 (58%)	6 (25%)	4 (17%)	0 (0%)
-breathlessness	12 (50%)	7 (29%)	4 (17%)	1 (4%)
-chest pain	9 (45%)	8 (40%)	3 (15%)	0 (0%)
Control arm				
-cough	10 (43%)	6 (26%)	6 (26%)	1 (4%)
-breathlessness	10 (42%)	8 (33%)	4 (17%)	2 (8%)
-chest pain	7 (37%)	8 (42%)	3 (16%)	1 (5%)

Hemoptysis	Complete relief	No relief
-Arm A (study arm)	5	0
-Arm B (control arm)	4	0

Assessment of Tumor Response

DISEASE STATUS	ARM A (study arm)	ARM B (control arm)
Partial response	21 (60%)	17 (49%)
Stable	9 (26%)	11 (31%)
Progression	5 (14%)	7 (20%)

NO. OF PATIENTS HAVING TOXICITY			
	After Week 1	After Week 2	After 4 weeks of treatment completion
ARM A (study arm)			
-haemoglobin	3	3	3
-total leukocyte count	0	0	0
-platelets	0	0	0
-skin reactions	0	4	1
ARM B (control arm)			
-haemoglobin	4	4	4
-total leukocyte count	0	0	0
-platelets	0	0	0
-skin reactions	0	5	2

DISCUSSION
Lung cancer is the most frequently diagnosed cancer with the highest reported cancer deaths worldwide. More than half of the non-small cell lung cancer cases present with metastasis at initial presentation. Palliative radiotherapy to the primary tumour has been a mainstay in the management of several tumour-related symptoms which have provided the patients with relief in their distress and improved their quality of life, however, may not have contributed in better survival rates. Addition of chemotherapy concurrently with palliative radiotherapy may have theoretical advantages of better symptomatic control and quality of life in these patients.

The patients enrolled in this study included 77% and 83% males in study and control groups, respectively. This can be compared with the lung cancer statistics in India[1] with an incidence of 58,970 cases in men out of a total cases of 81,748 which constitutes approximately 72%. A male predominance was also noted by Choudhary CR et. al.[4] in their institution-based study on the epidemiological profile of lung cancer in Western Rajasthan where the male-to-female ratio was 5.8:1.

1862 lung cancer patients were evaluated over a period of 10 years by Mohan et. al.[2] Most of the patients were in the age group of 46–70 years, with mean age of 58±11.1 years. Noronha, V et. al.[5] also

observed that the median age of the patients in their study was 56±11.87 years between 30 and 80 years in a total of 489 patients with around 92% patients were of non-small-cell carcinoma lung (NSCLC). In our study, mean age was 57.97 years and 60.34 years in the study group and control group, respectively, which is similar to the above studies.

A history of tobacco smoking was observed in 32(91%) patients in the study group and 34(97%) patients the control group. Tobacco smoking is responsible for 80% and 85-90% of lung carcinoma cases as observed by Mohan et. al.[2] and Alberg AJ et. al.[6], respectively. The number of adenocarcinoma and squamous cell carcinoma cases were comparable in both the groups in this study, though adenocarcinoma remains the most common histology in lung cancer patients in the general Indian population as studied by Nath et. al.[7]

Cough and breathlessness were the most common symptoms at initial presentation in both the study and control groups consisting of 69% and 66% patients in each group. Chest pain was present in 57% patients in study group and 54% patients in control group. Kuo CW et. al[8] noted that cough is the most common symptom present in 50% to 75% lung cancer patients at initial diagnosis, followed by dyspnoea in approximately 25% cases, and chest pain in approximately 20% cases. Also reported by Kocher F et. al.[9], 50 to 75% of patients with lung cancer present with cough, 25 to 40% of patients with dyspnoea and 20 to 40% of patients with chest pain at the time of diagnosis. On comparison, a greater number of patients presented with thoracic symptoms in our study.

58% patients in the study group and 43% patients in the control group had >50% subjective relief in cough (p=0.468). 50% patients experienced >50% subjective relief in the study group, and 42% patients experienced >50% subjective relief in the control group in breathlessness (p=0.772). In terms of subjective relief in chest pain, 45% patients experienced >50% subjective relief in the study group. In the control group, 37% patients had >50% subjective relief (p=0.848). No statistically significant difference was observed for relief in cough, breathlessness and chest pain (p>0.05). Our results are nearly similar to the study conducted by Vasant et. al.[10] that evaluated the role of cyclophosphamide with palliative radiotherapy in non-small cell lung carcinoma patients versus treatment with palliative radiotherapy alone. The study reported >50% relief in cough in 59% and 25-50% relief in 26% patients in the group that was given oral cyclophosphamide compared with the other group with 37% and 26% patients having >50% and 25-50% relief in cough, respectively. (>50% relief, p=0.194; 25-50% relief, p=1.00). 46% and 27% patients had >50% relief in breathlessness (p=0.193) and 29% and 46% patients had 25-50% relief (p=0.253) in the study and control group, respectively. 53% and 26% patients had >50% relief in chest pain (p=0.097) and 47% and 53% patients had 25-50% relief (p=0.746) in the group that received cyclophosphamide with palliative radiotherapy and palliative radiotherapy alone, respectively. The results were better in the former group in terms of symptomatic relief but not statistically significant (p-value>0.05). In a RCT conducted by Nawrocki et al.[11] consisting of incurable stage III NSCLC patients treated with radiotherapy alone vs. radiotherapy concurrently with chemotherapy (Vinorelbine and cisplatin). Both arms showed improved symptomatic control. Pain relief was seen in 67% of patients after RT alone vs 85% after chemo-RT, cough was controlled in 76% after RT alone vs 82% after chemo-RT. Moderate or severe dyspnoea was reported by only in a few patients after therapy in both arms.

Vasant et. al.[10]observed a statistically significant difference (p<0.001) in their study in which the patients assigned to radiotherapy with cyclophosphamide arm had a pre and post treatment median FACT-G scores of 61 and 76, respectively as compared to FACT-G scores of 61 and 67 in the radiotherapy alone arm. In a study conducted by Langendijk JA et. al.[12] to evaluate the changes in respiratory symptoms and quality of life (QoL) after thoracic radiotherapy, EORTC QLQ-C30 and EORTC QLQ-LC13 were used to investigate changes in QoL. Improvement in global QoL was in 37% of the cases. In our study, the patients were evaluated for quality of life based on the FACT-G scores after 4 weeks of completion of treatment. The mean FACT-G scores in the study group pre and post treatment were 63.44 and 72.05 respectively (p=0.261). In the control group, the mean FACT-G scores pre and post treatment were 59.58 and 64.12 respectively (p=0.448). There was a slight improvement in the quality of life in both the groups that was not statistically significant (p>0.05).

In our study, both the groups had comparable tumour response after treatment. 5 participants (14%) had progression of their tumour, 21 participants (60%) had a partial response, and 9 participants (26%) had stable disease in the study group. The control group had 7 participants (20%) with progression, 17 participants (49%) with a partial response, and 11 participants (31%) with stable disease (P-value of 0.621). Therefore, no significant difference in tumour response was found between the two groups. Revannasiddaiah et al.[13] in their study observed that the response rates were improved in patients receiving metronomic oral cyclophosphamide with palliative RT in NSCLC cases in comparison to patients receiving palliative RT alone (41.9% vs. 33.9%), though the results were not statistically significant (P=0.3831). This enhanced response rates was noted more in patients of adenocarcinoma histology (55.2% vs. 34.6%, p=0.1767). No such comparison in response rates in terms of histology was evaluated on our study. As also observed by Revannasiddaiah et al.[13], oral cyclophosphamide at a dose of 50 mg per day in addition to radiation as well as for prolonged periods did not have much impact on hematological toxicity which is similar to our study.

CONCLUSION

Metastatic NSCLC patients may be subjected to treatment with either palliative systemic therapy, palliative radiotherapy or best supportive care depending on their performance status, expected life expectancy, duration of treatment, and need for urgent intervention among various other factors. Our study showed improved symptomatic relief in terms of cough, breathlessness and chest pain and better quality of life post-treatment in the study group as compared to the control group but was not statistically significant. In conclusion, the results of our study indicate that palliative radiotherapy with concurrent cyclophosphamide in metastatic non-small cell lung cancer patients is a feasible and tolerable option in terms of symptomatic relief and quality of life. However, it shall require a larger sample size, longer duration of follow-up and better radiation techniques in order to arrive at a concrete conclusion.

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