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Original Article

Concurrent Hyperfractionated Chemoradiation Versus Conventional Fractionated Chemoradiation with Low-dose Weekly Paclitaxel in Locally Advanced Non–Small-Cell Lung Cancer in a Tertiary Cancer Center in Kashmir: A Prospective Study

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Abstract

Introduction: Lung cancer is the most common cancer worldwide and has a poor prognosis but integration of chemoradiation has led to an increase in overall survival time and percentage of cured patients with acceptable toxicity.

Purpose: The purpose of this study was to compare the efficacy of hyperfractionated (HFX) radiotherapy with conventional radiotherapy and weekly concurrent paclitaxel in stage IIB/III non-small-cell lung cancer (NSCLC).

Materials and Methods: A total of 60 patients were enrolled, of which 30 patients were given twice daily radiotherapy (1.2 Gy each) to a total of 72 Gy over 5–6 weeks and 30 patients were given single daily fraction (2 Gy) to a total of 66 Gy for the same duration to achieve a comparable biological effective dose. Both groups received weekly 50 mg/m^2 paclitaxel.

Results: An overall response of 83.3% versus 56.6% with a partial response of 70% versus 53.3% and complete response (CR) of 13.3% versus 3% was seen in HFX radiotherapy versus conventional radiotherapy which was statistically significant (P = 0.04). 10 of 25 patients and 11 of 17 patients who achieved response in study and control groups, respectively, progressed. The median survival of patients in HFX radiotherapy arm was 18 months, compared to 9 months in conventional radiotherapy arm. The median time to local recurrence was 19 versus 11 months with local recurrence-free survival of 72% versus 66% at 1 year follow-up. The 1 and 2 year survival rates were 76% and 40% in study arm and 50% and 26% in control arm (P - 0.005). Esophagitis (70% vs. 63.3%), skin reaction (70% vs. 63.3%), and radiation-induced pneumonitis (50% vs. 43.3%) were the common toxicities with no statistical significance between the two groups. Overall, there was mild chemotherapy-related toxicity.

Conclusions: The combination of HFX radiation with weekly paclitaxel is effective treatment with a moderate degree of toxicity in stage IIB/III NSCLC. An average response to treatment and the use of lesser drugs have made us to consider this therapy in locally advanced NSCLC.

Key words: Conventional radiotherapy, Hyperfractionated radiotherapy, Non-small-cell lung cancer, Paclitaxel

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INTRODUCTION

Lung cancer is the most common cancer worldwide, accounting for 13% of all new cases and 19% of cancer-related deaths worldwide.[1] Lung carcinoma is the second most common cancer diagnosis by gender, behind prostate cancer for men and breast cancer for women.[2] The

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estimated new cases of lung cancer in the US for 2018 are 234,030.[2] In India, lung cancer constitutes 6.9% of all new cancer cases and 9.3% of all cancer-related deaths in both the sexes.[3] GLOBOCAN estimate of lung cancer in India would indicate that the incidence of lung cancer in India is 70,275 (for all ages and both the genders).[4] In Kashmir, the annual crude incidence rate of lung cancer was 4.005 per 100 000 population, being 6.55/100 000 in males and 1.18/100 000 in females.[5]

Survival of people with lung cancer varies depending on the stage of cancer at presentation. Despite advances in imaging techniques and treatment modalities, the prognosis of lung cancer remains poor, with 5-year survival of 14% in early stages and <5% in locally advanced stages.[6,7] Unfortunately, only 20–30% of patients present with an operable disease, while most of the patients present in an advanced stages II and III.[8]

There are two main types of lung cancers. Around 20–25% are small-cell lung cancers (SCLCs) and 75–80% are non-SCLCs (NSCLCs).[9] The main types of NSCLC are squamous cell carcinoma (32%), adenocarcinoma (26%), and non-small-cell not otherwise specified (35%).[10] In India as well as Kashmir Valley, in particular, squamous cell lung cancer predominates still over adenocarcinoma.

Patients with stage III NSCLC are those who after clinical or surgical staging (or both) have no demonstrable distant metastasis but, at the same time, have locally extensive or invasive disease or involvement of mediastinal lymph nodes. If tumor can be completely resected, surgery provides the best chance of cure, but majority of patients are inoperable/unresectable at presentation. This group typically includes those with bulky stage IIIA disease and IIIB disease, excluding malignant pleural effusion.

Chemotherapy (CHT) has widely been used along with radiation, as multimodality therapy in the treatment of locally advanced NSCLC. Integration of chemoradiation has led to an increase in overall survival time and percentage of cured patients. Chemotherapeutic agents cover systemic disease while radiation treats the locoregional disease. Besides, many chemotherapeutic agents have radiosensitizing action even at low doses. Several phase III trials testing simultaneous (concurrent) chemoradiation versus radiation alone showed an increased survival in concurrent chemoradiation arm.

Platinum-based agents, especially cisplatin, have traditionally been used as chemotherapeutic agents concurrent with radiation. These can be used as weekly or daily basis. Although radiosensitizing action of cisplatin is well documented, it has many toxicities. Introduction of newer drugs has demonstrated high response rates with favorable toxicity profiles.[11] The role of paclitaxel as radiosensitizer has been widely appreciated due to its comparative low toxicity profile when given at low doses and good activity against NSCLC. Paclitaxel, a plant product, promotes microtubule assembly and stabilizes microtubules.[12] It causes cell arrest in G2M phase which is the most radiosensitive phase in cell cycle. Hence, it gives more time for radiation to act on cancer cell and increase the overall efficacy of radiotherapy.

Fraction size is also a dominant factor in determining late effects; overall treatment time has little influence. By contrast, fraction size and overall treatment time both determine the response of acutely responding tissues. The delivery of total dose in a large number of fractions than conventional fractionation is called hyperfractionation. The rationale underlying hyperfractionated (HFX) radiotherapy is that late responding tissues are generally more sensitive to large fraction sizes (low alpha/beta ratio), but many rapidly growing tumors remain sensitive even at low fraction sizes. This is offset by the increased tumor repopulation that occurs after 3–5 weeks. Hyperfractionation treatments are generally delivered as two treatments per day, often with a slightly higher overall dose than conventional fractionation to account for the reduction in cell kill that occurs with smaller fraction sizes.

MATERIALS AND METHODS

A total of 60 patients with histologically documented non–small-cell (non-adenoca) lung cancer with locally advanced/unresectable stage II (unresectable) and stage III A/B lung cancer were included in the trial (30 each in study and control group) prospectively between December 2012 and July 2016. Pre-treatment evaluation included history, physical examination, complete blood count (CBC), liver function test, kidney function test, contrast-enhanced computed tomography (CECT) chest and abdomen, pulmonary function test, and bone scan.

The inclusion criteria were histologically documented stage II (unresectable) and stage III A/B NSCLC (non adeno), age >18 years, the Eastern Cooperative Oncology Group (ECOG) performance status ≤2, adequate bone marrow function at presentation, serum chemistry within normal range, and optimal lung function, namely forced expiratory volume in 1 s/vital capacity ratio ≥75% and weight loss <5% during 3 months before diagnosis. The exclusion criteria were synchronous second malignancy, pregnancy or lactation, any comorbidity, distant metastasis, previous history of CHT or thoracic radiation, and malignant pleural effusion.

The control group comprised of cases who received conventional radiation with concurrent paclitaxel. To make study and control groups, comparable inclusion and exclusion criteria for both groups were the same.

After enlisting the patients, written consent was taken from all the patients. In the study arm (Group I), treatment schedule comprised of HFX radiation therapy (RT) concurrent with paclitaxel. HFX treatment consisted of two daily fractions of 1.2Gy/Fr, 5 days/week, with a minimum interfraction interval of 6 h. The initial target volume was treated with a dose of 48 Gy/4 weeks, after which a supplement dose of 24 Gy/2 weeks was delivered by reduced portals. CHT comprised of weekly injection paclitaxel at 50 mg/m^2 (1 h infusion) given with premedication on day 1 of every week of radiation. Radiation was delivered on a cobalt-60 teletherapy machine. The primary tumor with a margin of 2 cm, the ipsilateral hilum with 2 cm margin, contralateral hilum with 1cm margin and mediastinum was irradiated in phase 1. the ipsilateral hilum encompassed with a 2-cm margin and the contralateral hilum with a 1 cm margin. The ipsilateral supraclavicular fossa was included in the treatment field only when the primary tumor was located in the upper lobe. In the control arm (Group II), CHT was given in similar manner and radiation was delivered by conventional fractionation, i.e., initial target volume by 2 Gy/Fr for a dose of 46 Gy/23 Fr, followed by supplement dose of 20 Gy/10 Fr by reduced fields. In both groups, the biological effective dose was comparable and treatment was completed within 6–8 weeks. During the period of chemoradiation, patients were monitored for signs and symptoms of toxicity. Treatment was stopped at Grade 3 non-hematological and Grade 4 hematological toxicity. At completion of treatment, patients showing progressive disease, stable disease, or partial response (PR) were assessed for consolidation CHT /salvage surgery as per departmental protocol, depending on their performance and disease status.

After completing treatment, patients were followed up every month for 3–4 months and then examined after every 10–12 weeks for late toxicities (as per RT oncology group [RTOG] criteria) along with assessment for local and systemic recurrences. On each follow up the common expected toxicities like pneumonitis, esophagitis, mucositis, and neutropenia were checked. On each follow-up, CBC, blood chemistry, and chest-X ray were done. Treatment response was assessed by clinical examination, CT chest, and abdomen. The criteria for treatment response were performed as per the RECIST 1.1 criteria.[13]

Statistical Analysis

The results of the two groups were compared using statistical analysis. Differences, if any, between pairs of groups in patient characteristics, response rates, and incidence of toxicity were evaluated by Chi-square test. Overall and relapse-free survival rates were calculated the Kaplan–Meier method. $P < 0.05$ was considered to be statistically significant.

RESULTS

A total of 60 patients were available for final analysis, 30 in study arm and 30 in control arm; The mean age was 62.5 ± 12.5 years in study group and 60.2 ± 11 years in control group. 26 of 30 (86.7%) patients in study arm were smokers. Cigarette smoking was predominantly found in 17 patients (56.6%), of which 10 patients (33.3%) smoked only cigarettes and 7 patients (23.3%) were addicted to both huqa and cigarettes. In the control arm, 90% of patients were smokers. Cigarette smoking was seen in 16 patients (53.3%), of which 10 (33%) smoked only cigarettes and 6 (20%) were addicted to both huqa and cigarettes. ECOG score was I in 56.6% and II in 33.3% in study group and was I in 50% and II in 36.6% in control group. Well-differentiated squamous cell carcinoma (W/D Sq cell ca) was slightly more than moderately D Sq cell ca (M/D Sq cell ca) (46.7% vs. 40%) in study arm, whereas M/D Sq cell ca was more than (66.7% vs. 38.3%) W/D Sq cell ca in control group. Poorly differentiated squamous cell carcinoma was only 13.3% and 3% in study and control groups, respectively. Right lung disease was seen more (53.3%) compared to the left lung (46.6%) in study group, whereas there was no difference (50% in each group) in control arm. The most common symptoms in both the study and the control arms were a cough with expectoration (70%) followed by hemoptysis (61.7%). 80% (24 of 30) in study group had a cough with expectoration as compared to 60% (18 out of 30) in control group. However, many cases had more than one symptom in both the groups. In both arms, stage IIIB was predominant, accounting for 46.6% and 50% in study and control arms, respectively, compared to stage IIIA (40% vs. 36.6%) and stage IIB (13.3% vs. 13.3%). Most of patients belonged to T2 subset (40% in study arm and 36.6% in control arm) and N2 subset (53.3% in study arm and 40% in control arm) in both the arms. The main patient and tumor characteristics are presented in Table 1.

Survival, Response, and Relapse

To evaluate objective response, radiological tests (chest X-ray and/or CECT chest) were done using RECIST 1.1 criteria.[13] In the HFX arm, 21 patients showed a PR (70%) and four patients had CR (13.3%) with an overall response of 83.3% (25 of 30). The remaining 5 patients (16.6%) failed to show response, of which three patients (10%) had stable disease (SD) and 2 patients (6%) had a progression of disease (PD) during chemoradiation. In the conventional

group, only 17 patients (56.6%) showed overall response, of which 16 patients (53.3%) showed PR and one patient (3%) showed CR. Of the 13 patients (43.3%), 9 patients (30%) had SD and 4 patients (13.3%) had PD. After comparing both groups by Chi-square analysis, overall response was statistically significant ($P = 0.04$) in the study group than control group. In the study group, of 25 patients who achieved response, 10 patients (40%) developed recurrence of disease in the form of local PD or distant metastasis during follow-up (6 patients had intrathoracic PD, 2 had only distant metastasis, and 2 patients had both local recurrence and distant metastasis). In the control group, of 17 patients who achieved response, 11 patients (64.7%) had PD during follow-up (8 patients had local recurrence, 2 patients had distant metastasis, while 1 patient had both local and distant metastasis [Tables 2 and 3].

Survival analysis was performed using Kaplan–Meier method. The log-rank test was used for between-group comparisons. The median survival of patients in study arm was 18 months with 95% confidence interval (CI) of 9.98–26.02 months, whereas median survival of controls was 9 months with 95% CI of 6.96–11.03 months. Overall median survival of both groups was 12 months with 95% CI of 5.23–18.76 months. The 1-year survival rate in study arm was 76%, whereas in control group, it was 50%, and 2-year survival rate was 40% in study group and 26% in control group. The log-rank test between the two did reveal a statistical significance with a $P = 0.005$ [Figure 1].

Table 1: Patient characteristics

Characteristics	Study arm	Control arm
Total number of patients	30	30
Age (years)		
Mean	62.5	60.2
Range	44–74	42–72
Sex		
Male	28	25
Female	2	5
Smoking habits		
Smokers	26	27
Non smokers	4	3
Histology		
W/D squamous	14	9
M/D squamous	12	20
P/D squamous	4	1
Stage		
IIB	4	4
IIIA	12	11
IIIB	14	15
ECOG (performance status)		
0	3	4
1	17	15
2	10	11

WD: Well-differentiated, MD: Moderately differentiated, PD: Poorly differentiated

Prognostic Factors for Response

Analysis of 25 patients who achieved treatment response (PR+CR) in concurrent HFX arm showed that group of patients with ECOG performance score 2 had a response of 60%. Patients with lower ECOG score had better response rate: 100% for ECOG of 0 and 88.2% for ECOG of 1. The trend was the same in concurrent conventional arm with only 18.1% response in patients with ECOG 2 and 73.3% in ECOG 1. Similarly, patients in stage IIB showed better response (100% in study and 75% in control arm). Stage IIIB patients achieved a comparatively poor response in both the arms (78.5% vs. 46.7%) than stage IIIA (83.8% and 63.6%) in study and control groups, respectively. The patients with younger age groups also achieved better response, and it decreased with increasing age.

Toxicity

Treatment-related toxicity was assessed by RTOG toxicity scoring criteria. Esophagitis was the most common complication seen in both the study and control arms. In the study arm, 70% of patients suffered from esophagitis (Grade 1 - 30%, Grade 2 - 30%, and Grade 3 - 10%), whereas, in control arm, 63.3% of patients suffered from esophagitis, of which 20% had Grade 1 and 40% had Grade 2 esophagitis. Radiation-induced skin reaction was seen more (70%) in study arm than control arm (63.3%). Grade 3 skin toxicity was also more in study arm than control arm (13.3% vs. 0%).

Table 2: Distribution of patients according to their response to treatment

Response to treatment	Study group, *n*=30	Control group, *n*=30	Statistical remarks (*P* value)
	n (%)	*n* (%)	
Overall response			
Partial response, PR	21 (70)	16 (53.3)	0.075(NS)
Complete response, CR	4 (13.3)	1 (3)	
Stable disease, SD	3 (10)	9 (30)	
Progression of disease, PD	2 (6)	4 (13.3)	
Overall response (PR+CR)	25 (83.3)	17 (56.7)	0.04 (Sig.)
PD+SD	5 (16.7)	13 (43.3)	
Total	30 (100)	30 (100)	

PR: Partial response, CR: Complete response, SD: Stable disease, PD: Progression of disease

Table 3: Distribution according to the pattern of failure in patients who achieved initial response

Failure pattern	Study group, *n*=25	Control group, *n*=17	Statistical remarks (*P* value)
	n (%)	*n* (%)	
Intrathoracic progression of disease			
Intrathoracic progression only	6 (24)	8 (47.0)	0.44 (NS)
Intrathoracic progression+distant metastasis	2 (8)	1 (5.8)	
Distant metastasis only	2 (8)	2 (11.7)	
Total	(10)	11 (64.7)	

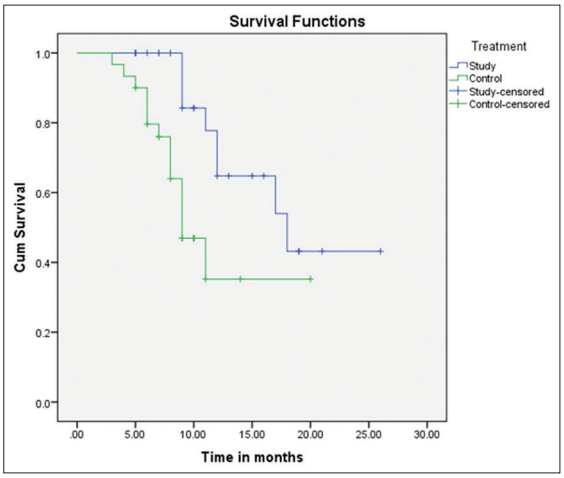

Figure 1: Disease free survival (months)

Stomatitis was seen more in control arm than study arm (43.3% vs. 33.3%). The incidence of upper GI toxicity (nausea and vomiting) was also low (43.3%) in study arm than in control arm 33.3% with no Grade 3 toxicity. Overall, hematological toxicities were mild and were almost similar in both the arms with no Grade 3 toxicity in any arm. Radiation-induced pneumonitis was more in study group than control group. Neuropathy was almost similar in both study and control groups.

There was no Grade 4 toxicity or toxicity-related death (Grade 5 toxicity) in any group [Table 4].

DISCUSSION

Locally advanced (stage IIB and stage III) NSCLC is considered to be non-resectable in majority of patients. The role of surgery with or without CHT or RT has been placed under scrutiny in recent trials, and it seems to offer no clear advantages in terms of survival.[14,15] Although some patients might benefit from it, these patients represent a very small proportion. Once surgery has been ruled out, the best treatment currently available is CHT combined with RT. The superiority of this combination over RT alone was demonstrated several years ago.[16-18] The first trial to demonstrate a survival advantage with the addition of CHT to radiation was reported by Dillman *et al.* and was conducted by cancer and leukemia Group B-8433.[19] It showed a median survival of 13.8 months in chemoradiation arm and 9.7 months in radiation only arm ($P = 0.0066$). The respective 1-, 2-, and 3-year survival rates in chemoradiation arm were 55%, 26%, and 23%, respectively. The same survival rates in radiation only group were 40%, 13%, and 11%, respectively. In 7 years' follow-up, this improved survival in chemoradiation arm was shown to persist.[19] After several other studies confirmed the superiority of adding CHT to radiation, combined chemoradiation became the standard in locally advanced NSCLC which led the American Society of Clinical Oncology to issue guidelines in 1997 and recommended the use of chemoradiation in locally advanced NSCLC.[20]

After the advantages of chemoradiation were established beyond doubt, next question was the timing and sequencing of CHT with respect to radiation, whether to give CHT before, after, or even during radiation (sequential/concurrent). The main advantage with concurrent chemoradiation is an effect on micrometastasis as well as enhances radiotherapeutic effect on local tumor through radiosensitization. The most recent randomized trials studying the integration of CHT and RT have shown an improved survival with concurrent CHT and RT regimens.[16,17]

On the basis of radiobiological considerations, different investigators introduced alternative fractionation schedules for the treatment of locally advanced NSCLC so as to further intensify the local efficacy of radiotherapy. Being influenced largely by the RTOG study 8311 design,[21] various studies were done on HFX radiotherapy in NSCLC, showing better local control and overall survival. To investigate the efficacy of concurrent HFX RT and low-dose CHT in stage III NSCLC, a study was conducted by Jeremic *et al.*[22] showing a median survival of 22 versus 14 months and 4-year survival rates of 23% versus 9% ($P = 0.021$). The two groups showed a similar incidence of acute and late high-grade toxicity ($P = 0.44$ and 0.75, respectively). No treatment-related deaths were observed during this study.

Although the benefit of concurrent chemoradiation over sequential chemoradiation was established, concurrent modality was associated with higher toxicity rates. The main toxicities observed were hematological toxicities and radiation-induced esophagitis.[23] Thus, efforts were made to decrease the overall toxicity in concurrent modality with newer drugs like platinum compounds. The other issue is the optimal dose in concurrent modality, whether to give

Table 4: Distribution of patients according to toxicity observed (RTOG criteria)

Toxicity	Grade	Study group, *n*=30	Control group, *n*=30	Statistical remarks
		n (%)	*n* (%)	
Stomatitis	1	5 (16.7)	8 (26.7)	0.563 (NS)
	2	4 (13.3)	5 (16.7)	
	3	1 (3.3)	0 (0)	
	4	0 (0)	0 (0)	
	Total	10 (33.3)	13 (43.3)	
Esophagitis	1	9 (30)	6 (20)	0.551 (NS)
	2	9 (30)	12 (40)	
	3	3 (10)	1 (3.3)	
	4	0 (0)	0 (0)	
	Total	21 (70)	19 (63.3)	
Upper GIT (nausea/vomiting)	1	5 (16.7)	8 (26.7)	0.563 (NS)
	2	5 (16.7)	5 (16.7)	
	3	0 (0)	0 (0)	
	4	0 (0)	0 (0)	
	Total	10 (33.3)	13 (43.3)	
Skin reaction	1	11 (36.7)	13 (43.3)	0.198 (NS)
	2	5 (16.6)	4 (13.3)	
	3	4 (13.3)	0 (0)	
	4	0 (0)	0 (0)	
	Total	20 (70)	17 (56.6)	
Hematological				
Leucopenia	1	3 (10)	7 (23.3)	0.378 (NS)
	2	2 (6.7)	2 (6.7)	
	3	0 (0)	0 (0)	
	4	0 (0)	0 (0)	
	Total	5 (16.6)	9 (30)	
Neutropenia	1	5 (16.7)	4 (13.3)	0.718 (NS)
	2	0 (0)	0 (0)	
	3	0 (0)	0 (0)	
	4	0 (0)	0 (0)	
	Total	5 (16.6)	4 (13.3)	
Anemia	1	2 (6.7)	4 (13.3)	0.431 (NS)
	2	1 (3.3)	0 (0)	
	3	0 (0)	0 (0)	
	4	0 (0)	0 (0)	
	Total	3 (10)	4 (13.3)	
Thrombocytopenia	1	0 (0)	1 (3.3)	0.313 (NS)
	2	0 (0)	0 (0)	
	3	0 (0)	0 (0)	
	4	0 (0)	0 (0)	
	Total	0 (0)	1 (3)	
Pneumonitis	1	8 (26.7)	6 (20)	0.685 (NS)
	2	6 (20)	7 (23.3)	
	3	1 (3.3)	0 (0)	
	4	0 (0)	0 (0)	
	Total	15 (50)	13 (43.3)	
Neuropathy	1	4 (13.3)	5 (16.7)	0.936 (NS)
	2	1 (3.3)	1 (3.3)	
	3	0 (0)	0 (0)	
	4	0 (0)	0 (0)	
	Total	5 (16.6)	6 (20)	

RTOG: Radiation therapy oncology group, GIT: Gastrointestinal

lower radiosensitizing dose or standard dose of systemic CHT. Although the latter dose is associated with better response rates but very high toxicity, it might be better to give lower doses of CHT with good radioenhancing action. In this regard, paclitaxel has demonstrated promising results.

Paclitaxel, a complex plant product (diterpene) extracted from the bark of *Taxus brevifolia*, has demonstrated substantial anticancer activity in patients with advanced (stage IIIB or IV) non-small-cell lung cancer. In addition to the radiosensitizing effect, it produced a response rate of 20–25% when given alone, as described by investigators from three different institutions.[24] Paclitaxel has a unique mechanism of action, binds to tubulin, enhances rate and extent of microtubular polymerization, and stabilizes formed microtubules, hence causing cell arrest.[25] The cell

arrest caused by paclitaxel happens in G2 and M phase of cell cycle which are most sensitive to radiation effect. The dose of paclitaxel was weekly 50 mg/mt^2, although phase I trials have demonstrated that up to 60 mg/mt^2 of paclitaxel can be given with quite acceptable side effects in concurrent settings.[26] The activity of paclitaxel in advanced NSCLC and its strong radiosensitizing properties provided the basis for its use in concurrent chemoradiation in locally advanced NSCLC.[27]

In our setup, patients present mostly in a cachexic state with poor performance status. In an earlier study conducted to assess the profile of lung cancers in our hospital, it was found that 23% of patients opted for no treatment at all 22.4% received radiation alone followed by chemoradiation (14.9%) and CHT alone (9.4%).[28] Patients may be reluctant to receive CHT due to morbidities involved. For this reason, an attempt was made to demonstrate the benefits of concurrent chemoradiation with acceptable toxicity profile, the aim being minimal toxicity apart from attaining maximal benefit to patients.

In our study, majority of the patients were in the age group of 50–70 years, majority being males in both study and control groups (93.3% and 88.3%), respectively. The male-to-female ratio which is coming down in western literature due to an increasing trend of smoking in females was not seen in our study. Our study showed a ratio of 14:1 and 5:1 in study and control groups, respectively, possibly because smoking in females has not increased as in developed countries.[28,29] In our study, 86.7% were smokers in the study arm and 90% in the control arm. Smoking has long been established as a risk factor for lung cancer.[28-32]

Although approximately 10% of lung cancers are detected in asymptomatic patients on routine chest radiograph, most patients are symptomatic when diagnosed. The most common symptoms in our patients were cough with expectoration (80% in study and 60% in control arm), hemoptysis (66.7% in study and 56.7% in control), and breathlessness (36.7% in study and 40% in control arm) which were similar to other studies.[28-35] The right lung was involved in 16 patients (53.3%) in study arm and 15 patients (50%) in control arm as compared to left lung which was involved in14 (46.6%) in study arm and 15 patients (50%) in control arm, respectively. These results have been reported by other investigators as well.[28,33]

While studying a large group of 600 patients of NSCLC using concurrent HFX chemoradiation in stage II patients, Jeremić *et al.* have shown better outcome in squamous cell histology.[36] In our study, we had included only squamous histology. Well-differentiated squamous cell histology was more (46.7% vs. 40%) in study group, whereas moderately differentiated histology was more than well-differentiated (66.7% vs. 38.3%) in control group. Furthermore, most of the patients belonged to stage IIIB in both the groups, 46.6% in study group and 50% in control group. Patients with ECOG performance status of 2 or less were included in the present study. Most of the patients belonged to ECOG 1 category, 56.6% in study group and 50% in control group. Similarly, since pre-treatment weight loss is an important prognostic factor[37] and patients with weight loss of >5% carry a bad prognosis, patients with weight loss <5% were taken into the study.

Bronchoscopy was the main diagnostic modality and was positive for malignancy in 76% patients. There were only three patients (10%) positive for malignant cells (M cells) in bronchoalveolar lavage (BAL) in study group and 5 patients (16.6%) in control group which are quite low as compared to other studies where BAL was positive for M cells in 68% of patients.[33,38]

The short overall treatment time improved patient compliance for completing treatment as within 2 months whole radical CCRT was over. In our study group, only six patients defaulted early in study group and only 4 patients defaulted in control group; 30 patients in each group completed full treatment which was assessed for response and toxicity.

The present study showed an objective response rate (ORR) of 83.3% (25/30) patients in concurrent HFX chemoradiation arm, of which 4 (13.3%) patients showed CR, 21 (70%) patients showed PR, and 16.60% of patients failed to show response, i.e., they had either SD (10%) or their disease progressed (6%) locally during treatment. In the control arm, ORR was achieved in 56.6% (17/30) patients, of which only 1 (3%) patient showed CR and 16 (53.3%) had PR. The difference in overall response rates between the two arms was 26.7% in favor of concurrent HFX arm which was statistically significant ($P = 0.04$).

The median survival of patients in concurrent HFX chemoradiation arm was 18 months, compared to 9 months in concurrent conventional radiation arm. The survival advantage was 9 months in favor of concurrent HFX arm. The median time to local recurrence seen in study group was 19 months with local recurrence-free survival of 72%, whereas median time to local recurrence in control group was 11 months with local recurrence-free survival of 66% at 1 year follow-up. The 1-year survival rate in study arm was 76%, whereas, in control arm, it was 50% and a 2-year survival rate was 40% in study group and 26% in control group. The 3-year survival rate was 25% in study arm and 14% in control arm. The log-rank test between the two did reveal a statistical significance with $P = 0.005$.

After analyzing the response rates in different subsets of patients, it was noticed that ECOG status, age, and stage did have a bearing on it. Young patients with good ECOG, and lower stage of disease at presentation had better response in both groups. This was in consistent with other studies.[37]

Any treatment protocol is assessed by its toxicity profile which in turn determines patient compliance and subsequent response and survival rates. Radiation-related toxicities were assessed by RTOG toxicity scoring criteria. As far as our study is concerned, due to lower dose of paclitaxel, the toxicities were quite acceptable, and consequently, patient compliance was better. There was no Grade 4 toxicity and few Grade 3 toxicities. In particular, hematological toxicities were mild. This is in contrast to patients who receive conventional full-dose CHT, which is associated with high morbidity,[39] resulting in frequent disruptions and discontinuation of treatment. Esophagitis, induced by thoracic radiation, was the main complication observed, more in study group than control group (70% vs 63.3%) with no statistical significance(p=0.55) on comparison. This was inconsistent with most of the studies involving thoracic radiation. Chandra and Belani,[40] in 1999, have reported 26% of Grade 3–4 esophagitis and 16% pneumonitis in HFX radiation concurrent with paclitaxel and carboplatin. However, our study showed only 10% Grade 3 toxicity in study arm. Radiation-induced pneumonitis was also more in study arm than control arm (50% vs. 43.3%) with no significance (P = 0.685). In a multicenter phase II study, the RTOG enrolled 79 patients onto a protocol of HFX accelerated RT (1.2 Gy bid, total dose of 69.6 Gy) and their results showed Grade ≥3 lung toxicity in 19 patients (25%) accounting for two of three treatment-related deaths.[41] In contrast to that, our study had only one (3.3%) Grade 3 reaction in study arm. In our study, radiation-induced skin reaction was seen more (70%) in concurrent HFX arm than concurrent conventional arm (63.3%) with 13.3% Grade 3 toxicity in study arm compared to 0% in control arm. However, overall, no statistical significance was seen (P = 0.198).

In the present study, our results were comparable to other studies.[36,42] However, controversies remain over the most effective combination of drugs, their optimal mode of administration, optimal sequencing of radiation and CHT as well as details of thoracic radiation; these important issues have not been properly defined. A clinical trial cannot provide exact "prescription" of how to treat individual case; ultimately, treatment modality is to be decided by clinician and patient together and will depend on many factors: Survival, toxicity, quality of life, and economic burden.

CONCLUSIONS

The combination of HFX radiation with weekly paclitaxel is effective for the treatment of patients with advanced NSCLC. The moderate degree of toxicity, an average response to treatment, and use of lesser drugs have made us to consider this therapy in locally advanced NSCLC.

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