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Inter Comparison of Concurrent versus Sequential Chemo Radiation in Limited-Stage Small Cell Carcinoma of Lung in Kashmir, North India

KHURSHEED AHMAD PARA
Senior Resident, Internal Medicine
SKIMS, Srinagar
HILAL AHMAD DAR
Senior Resident, Internal Medicine
GMC Srinagar
MOHD DILAWAR MIR
Senior Resident, Ophthalmology
SKIMS Srinagar
SHIEKH AEJAZ AZIZ
Professor, Medical Oncology
SKIMS Srinagar
NAZIR AHMAD KHAN
Associate professor, Medical Oncology
SKIMS Srinagar
NISAR AHMAD SHEIKH
Senior Resident, Medicine
Apollo Hospital, Delhi
India

Abstract:

Purpose: *To evaluate the tumor response ,toxicity profile and survival rates between concurrent versus sequential chemo radiotherapy in limited-stage SCLC.*

Material and Methods*: 42 patients of SCLC were taken up for the study. Thoracic radiotherapy consisted of 45 Gy over 5 weeks , and the patients were randomized to receive either sequential or concurrent radiotherapy. All patients received six cycles of cisplatin plus etoposide every 3 weeks. Thoracic radiotherapy was begun on day 1 of the second cycle of chemotherapy in the concurrent arm and after third cycle in the sequential arm.*

***Results**: Complete response was seen in 66.7%, progression in 14.3% and partial response in 9.5% in concurrent arm, compared to complete response in 28.6%, partial response in 47.6 %, progression in 14.3% and no response (stable disease) in 4.8% respectively in sequential arm (P-value 0.075). Hematologic toxicity (febrile neutropenia p-value 0.022) ,gastrointestinal toxicity (nausea and vomiting , p-value 0.03) and neurologic toxicity (p-value 0.52) were more in concurrent arm compared to sequential arm.*

***Conclusion:** Tumor response favours concurrent chemo radiation, however results are not statistically significant but chemo morbidity (significant hematologic and gastrointestinal toxicity) were more in concurrent arm compared to sequential arm.*

Key words: Concurrent Chemo Radiation, Sequential Chemo Radiation, Limited-Stage Small Cell Carcinoma of Lung, Kashmir, North India

Introduction

Lung cancer was considered to be rare in the beginning of the century[1] but has now reached almost epidemic proportions. It is the leading cause of cancer deaths in developed countries and is also rising at alarming rates in developing countries[2]. Lung cancer is a major health problem in Kashmir valley and constitutes 9.9% of all cancers. It is the second common malignancy among males. Khan NA et al studied 321 patients in 2006 in Kashmir valley . There was preponderance of males (91.9%) as compared to females (8.1%).[3]

Histologically lung cancer is broadly divided into non-small cell lung cancer (85%) and small cell lung cancer (15-20%) [4]. Small cell lung cancer has faster tumor doubling time and higher incidence of distant metastasis at the time of diagnosis [4]. The most important known cause of SCLC is cigarette smoking [5]. Presenting symptoms in patients with SCLC can be constitutional, pulmonary, the result of extra thoracic spread,

or due to paraneoplastic disorders. In one series in which patient-reported symptoms were recorded using the Lung Cancer Symptom Scale, fatigue was the most common symptom with decreased physical activity, cough, dyspnea, decreased appetite, weight loss, and pain occurring sometime in the course of the illness in the majority of patients. Hemoptysis was noted in 14% in the same series. The primary tumor often presents as a large central mass invading or compressing the mediastinum. Superior vena cava obstruction is present at diagnosis in 10% of patients with SCLC, and in these cases, the symptoms are often worsened by associated thrombosis in the compromised blood vessel[6]. Bone involvement is usually characterized by osteolytic lesions, often in absence of bone pain or rise in serum alkaline phosphatase [7]. SCLC accounts 75% tumors associated SIADH[8]. Paraneoplastic neurologic disorders in SCLC include sensory, sensorimotor, autoimmune neuropathies and encephalomyelitis [9]. Preinvasive and in situ malignant changes are rare in SCLC [10]. A two-stage system, introduced by the Veterans' Administration Lung Study Group (VALSG) is used instead of TNM system [11]. In the VALSG system, limited stage is defined as disease confined to one hemi thorax that can be encompassed in a "tolerable" radiation field. All other patients are considered to have extensive-stage disease.

Material and Methods:

This prospective randomized comparative study was conducted in the department of Medical and Radiation Oncology, Sher-i-Kashmir Institute of Medical Sciences, Soura, Srinagar from July 2008 to October 2010 after approval from Ethical committee. Forty two patients with small cell lung carcinoma were taken for the study after informed written consent and randomized into two groups. Each patient underwent history,

clinical examination , baseline investigations, CECT chest and abdomen ,fiber optic bronchoscopy, biopsy and histopathological examination, bone scan and MRI/CT brain(to exclude brain metastasis).After completion of treatment, all patients underwent CT Brain to exclude brain metastasis before giving prophylactic cranial irradiation(PCI).Contrast enhanced cranial MRI was advised if PCI delayed more than four months after the chemo radiotherapy because overt brain metastasis may develop from subclinical disease during this time. CEMRI also indicated in patients having neurologic findings with normal CT brain imaging.

Inclusion criteria: Histopathological diagnosis of all limited stage SCLC disease with good performance status of ECOG 0 to 2, measurable disease ,normal haemogram and age ≤75 years,

Exclusion criteria: All patients having extensive disease, low performance status(ECOG 3 to 4), co morbid illnesses like chronic liver disease, chronic renal failure, symptomatic cardiac disease patients having h/o myocardial infarction in the past six months, prior cancer or cancer treatment, pregnant and lactating women were excluded.

Chemotherapy Radiotherapy: Thoracic radiotherapy was started on day 1 of the 2nd cycle of chemotherapy in concurrent group and after the completion of 3rd cycle of chemotherapy in sequential group. Radiotherapy was delivered by co^{60} unit (cobalt) for a total dose of 45 GY in 5 weeks .The radiotherapy was given for 5 days in a week with 1.53 -1.8Gy fractions in each day. The initial field included the primary disease site with 1.5 cm margin around the mass. After completion of radiotherapy, patients received 3 more cycles of chemotherapy in sequential arm and 4 more cycles of chemotherapy in concurrent arm. **:** Chemotherapy was given in every 21-day

cycle in both concurrent and sequential group. Chemotherapy consisted of cisplatin 75mg/m^2 IV on day1 and etoposide 100mg/m^2 on day 1, day 2 and day 3. If the leukocyte decreased below 3,000/mm^3, ANC ≤500 or the platelet count below 20,000/mm^2 on the first day of next cycle, chemotherapy was with held until the counts recovered and total six cycles were given.

Concurrent Arm

Sequential Arm

All patients were re-assessed at the end of treatment in the same manner as at the time of enrollment. Patients who showed complete response to initial treatment received prophylactic cranial irradiation. The brain irradiation consisted

of 25 GY in 1.5-GY fractions administered once daily, 5 days per week for 3 weeks by two lateral portals.

Tumor response and toxicity criteria: Tumor response and treatment toxicity were classified in accordance with the world health organization criteria [12,13]. A complete response (CR) was defined as the disappearance of all clinical evidence of the tumor. A partial response (PR) was defined as a decrease of 50% or more in the product of the length and width of any measureable tumor. A stable disease (SD) was defined as a less than 50% decrease or a less than 25% increase. A progressive disease was defined as an increase of more than 25% or appearance of new tumor [14].

Study design and analysis: This study was a prospective randomized comparative study. The primary end point was tumor response, toxicity profile and secondary end point was overall survival and progression-free survival . Duration of survival was measured from date of enrollment up to the date of death [15]. Progression-free survival was measured from the date of enrollment to the date of the first observation of disease progression or death [15]. If there was no progression or the patient had not died, progression-free survival was censored at the date of confirmation of no progression.

Results:

Forty two patients were taken in this study. The age range of patients were from 45 to 75 years with mean age of 59.6 ± 8.67 years.

Age	**N**	**Mean ± SD**
Males	36	59.53 ±7.95
Females	6	57.67 ±13.079
Symptoms	**N**	**%**
Cough	38	90.50%
Hemoptysis	23	54.80%
Breathlessness	22	52.40%
Chest Pain	21	50.00%
Fever	8	19.00%
Hoarseness of voice	7	16.70%
Paraneoplastic manifestation	7	16.70%
Generalized weakness	6	14.30%
Weight loss	5	11.90%
Treatment Group	**n**	**%**
Group-I (Concurrent)	21	50%
Group-II (Sequential)	21	50%
Performance Status (ECOG)	**Group-I**	**Group-II**
1	15(71.40%	9(42.90%)
2	5(23.8%)	12(57.10%
3	1(4.80%)	0(0%)

Table 1: Demographic profile of the patients

The most common clinical manifestations were cough (90.5%) followed by hemoptysis (54.8%), breathlessness(52.4%) , chest pain (50%).and hoarseness of voice (16.7%). 42 cases with a histopathology documented small cell lung carcinoma (limited stage) were taken in the study and were randomized in concurrent arm and sequential treatment arm. 71.4% patients in group-I (concurrent group) had performance status 1 (ECOG) followed by performance status 2 in 23.8%and performance status 3 in 1.4% patients. Group-II (sequential group) had performance status 2 in 57.1% and performance status 1 in 42.9 % patients.

Table 2: Tumor Response According to Treatment Arm

Result	**Concurrent Arm**		**Sequential Arm**		**p value**
	n	%	n	%	0.075
Complete resolution	14	66.70%	6	28.60%	

Progression	3	14.30%	3	14.30%
Partial	2	9.50%	10	47.60%
No resolution	0	0%	2	4.80%

Complete response were seen in 66.7%, progression in 14.3% and partial response in 9.5% in concurrent arm, compared to complete response in 28.6%, partial response in 47.6 %, progression in 14.3% and no response in (stable disease) in 4.8% respectively in sequential arm.

Table 3: Treatment course & side effects between two groups of studied patients

				Group-I		Group-II		P-value
				n	%	n	%	
Treatment	Partial			2	9.5%	1	4.8%	
	Complete			19	90.5%	20	95.2%	1.0F
Side effects	Esophagitis	Grade 3		6	28.6%	3	14.3%	0.259
	Nausea &vomiting	Grade 1		6	28.6%	9	42.9%	
		Grade 2		5	23.8%	1	4.8%	
		Grade 3		8	38.1%	1	4.8%	0.03(sig)
	Diarrhea	Grade 1		7	33.3%	7	33.3%	
		Grade 2		3	14.3%	3	14.9%	0.99
		Grade 3		1	4.8%	1	4.8%	
	Cardiac side effects	arrhythmia's		3	14.3%	2	9.5%	
		Chest pain		1	4.8%	0	0%	0.519
	Neurologic side effects	peripheral neuropathy		5	23.8%	6	28.6%	
		Tinnitus		6	28.6%	3	14.3%	
		Alt. sensorium/encephalopathy		0	0%	2	9.5%	0.52
		Ataxia		2	9.5%	2	9.5%	
	Bone – marrow Toxicity	Febrile neutropenia	Grade1	8	38.1%	10	47.6%	
			Grade2	9	42.9%	4	19%	
			Grade3	3	14.3%	0	0%	0.022(sig.)
		Thrombocytopenia	Grade1	3	14.3%	15	71.4%	
			Grade2	10	47.6%	3	14.3%	0.001(sig.)
			Grade3	7	33.3%	1	4.8%	
			Grade 4	1	4.8%	0	0%	
		Anemia	Grade 1	2	9.5%	13	61.9%	
			Grade 2	12	57.1%	5	23.8%	0.000(sig)
			Grade 3	5	23.8%	0	0%	
			Grade 4	2	9.5%	0	05	
	Any other side effect	Infection		8	38.1%	4	19%	0.519
		Alopecia		17	81%	11	52.1%	0 .05

		Skin burns	5	23.8%	3	14.3%	0.432
		Mild to moderate azotemia	3	14.3%	3	9.5	0.519
Treatment-related deaths			1	4.8%	1	4.8%	1.0

With respect to side effect profile, sequential chemo radiation proved to be safer than concurrent chemo radiation. Hematologic ,gastrointestinal and neurologic toxicity were more in concurrent group compared to sequential group

Table 4: Progression Free and Survival time in months between two groups.

	Group	**Mean**	**Median**	**P-value**
Progression Free survival	Concurrent	17.956	19	
	Sequential	17.206	17	0.859
	Overall	15.248	20.752	
	Group	**Mean**	**Median**	**P-value**
Survival Time	Concurrent	21.552	27	
	Sequential	17.992	20	0.356
	Overall	19.669	20	

In this study mean and median progression free survival were 17.956 and 19 months in concurrent group compared to 17.206 and 17 months in sequential group with p-value of 0.859.Overall progression free survival was 20.752 months . Mean and median survival time were 21.55 and 27months in concurrent arm versus 17.992 and 20 months respectively in sequential arm but the difference was not statistically significant with p-value of 0.356.

Table 5 : Survival Time in Months (Kaplan-Meier Scale).

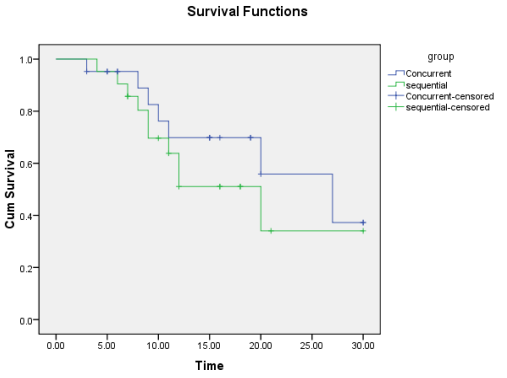
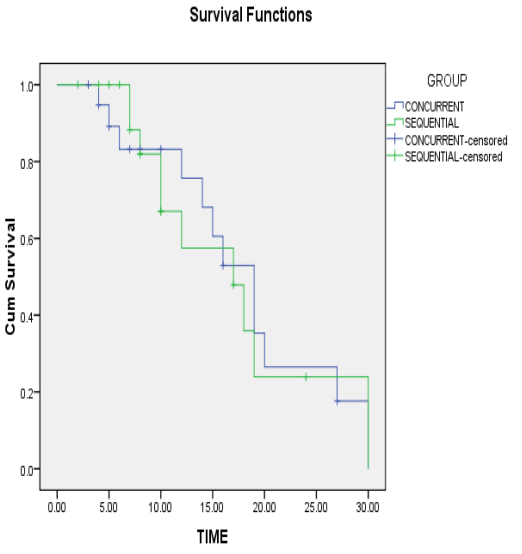


Table-6: Progression Free Survival (in months) of the studied patients in two groups.



Discussion

This study was conducted in the Department of Medical Oncology at Sher-i-Kashmir Institute of Medical Sciences,

Srinagar, J&K, India. It was a prospective randomized study. The study was conducted from May 2008 to October 2010. The aim of the study was to compare the tumor response ,toxicity profile and survival rates between concurrent versus sequential chemo radiotherapy in limited-stage small cell lung carcinoma. The age of the patients ranged from 45 to 75 years with a mean age of 59.67 ± 3.67 years, consistent with the study of Hasan Tathsoz et al [16], with a mean age of 58 ± 8.1 years. In the present study, the most common manifestations were cough (90.5%) followed by hemoptysis (54.8%), breathlessness(52.4%) chest pain (50%).and hoarseness of voice (16.7%) as also reported by Hasan Tathsoz et al [16]. Turrisi et al had determined that accelerated hyper fractionation, was superior to standard fractionation in an intergroup phase III study [17].

Early administration of thoracic radiotherapy may eliminate localized populations of chemotherapy-resistant tumor cells that might be responsible for treatment failure if permitted to disseminate systemically. This would be an obvious advantage of early administration of thoracic radiotherapy [18]. Cisplatin plus etoposide was found to be the optimal regimen for combination with concurrent thoracic radiotherapy [19, 20, 21].The median survival time with this regimen and concurrent twice-daily thoracic radiotherapy in the various phase II studies has been 18 to 22 months [22, 23, 24].

Comparison of tumor response ,progression free survival and overall survival in this study suggested that concurrent radiotherapy was more superior than sequential radiotherapy, but the difference was not statistically significant (p value 0.075) due to relatively small sample size of only 42 patients . Complete response were seen in 66.7%, progression in 14.3% and partial response in 9.5% in concurrent arm, compared to complete response in 28.6%, partial response in 47.6 %, progression in 14.3% and no response in (stable disease) in 4.8% respectively in sequential arm. This study demonstrated

improved tumor response compared to other studies but there was significant hematologic and gastrointestinal toxicity (p value 0.02 and 0.03 respectively). One reason may be 3 weekly cycle of chemotherapy in our study whereas Takada et al [25] used 4 weekly cycle of chemotherapy in concurrent arm. Another reason may be small sample size in our study. The median survival time in this study was 27 months in concurrent arm verses 20 months in sequential arm. Overall mean and median survival were 19.669 and 20 months respectively in limited stage small cell lung carcinoma. Takada et al[25]who conducted phase III study of concurrent versus sequential thoracic radiotherapy with cisplatin and etoposide for limited stage small cell lung carcinoma from 1991 to 1995.They reported that, concurrent radiotherapy yielded better survival than sequential radiotherapy (P = .097 by log-rank test). They reported that, Complete response 27%, partial response 65%, no change 3%, progression 4% in sequential arm compared to complete response 40%, partial response 57%, no change (stable disease) in 1%, progression 1% in concurrent arm. The median survival time was 19.7 months in the sequential arm versus 27.2 months in the concurrent arm.

Se-Hoon Lee et al[26] conducted a study of early concurrent chemo radiotherapy with prolonged oral etoposide and cisplatin for limited-stage small-cell lung cancer. They conducted a phase II trial of early concurrent CRT(chest radiotherapy), starting from the very beginning of the first cycle of chemotherapy for previously untreated limited stage small cell lung carcinoma. They gave conclusions that early concurrent CRT , starting from the very beginning of the first cycle of chemotherapy with prolonged oral etoposide and cisplatin failed to show any improvement in survival compared with other CRT regimens[26].

In the present study mean and median progression free survival was 17.956 and 19 months in concurrent group

compared to 17.206 and 17 months respectively in sequential group with p-value of 0.859. Overall median progression free survival was 20.752 months.

David S. Ettinger et al [27] observed the median progression-free survival time was 13 months in his study of paclitaxel, etoposide, and cisplatin chemotherapy combined with twice-daily thoracic radiotherapy for patients with limited-stage small-cell lung cancer.

Total ten deaths 47.6 % occurred up to 2 year follow up in concurrent arm compared to 14 deaths 66.7% in sequential arm. In the present study 2 year survival rate was 52.3% in concurrent group compared to 33.3% in sequential group. Takada et al [25] observed the 2, 3, and 5 year survival rates for patients who received sequential radiotherapy were 35.1%, 20.2%, and 18.3%, respectively, as opposed to 54.4%, 29.8% and 23.7%, respectively, for the patients who received concurrent radiotherapy.

Hematologic toxicity was more in concurrent arm compared to sequential arm. Grade 1,2 and 3 neutropenia occurred in 38.1%,42.9 and 14.3% in concurrent arm compared to 47.6%, 19% and 0% respectively in sequential arm with significant p-value of 0.022. There were no grade 4 neutropenia in each group. Grade 1,2,3 and 4 thrombocytopenia occurred in 14.3%,47.6%,33.3% and 4.8 % in concurrent arm compared to 71.4%,14.3%,4.8%and 0% respectively in sequential arm with significant p-value of 0.001. Grade 1,2,3 and 4 anemia occurred in 9.5%,57.1%,23.8% and 9.5% in concurrent arm compared to 61.9% , 23.8% and 0% respectively in sequential arm. There were no grade 3 and grade 4 anemia in group-II. Takada et al[25] observed grade 3 leucopenia in 44.5%, grade 4 leucopenia 9%, grade 3 thrombocytopenia 12%, grade 4 thrombocytopenia 13% , grade 3 anemia 42% ,alopecia 2%,infection 1% and treatment related death 4% in sequential arm versus grade 3 leucoopenia 50%, grade 4 leucopenia 37% , grade 3 thrombocytopenia

29%,grade 4 thrombocytopenia 7% , grade 3 anemia 54%, alopecia 2%,infection 1% and treatment related death in 3% respectively in concurrent arm [25].In our study, profile of side effect were consistent with Takada et al but percentage of side effects were more in our study. One reason may be 3 weekly cycle of chemotherapy in our study whereas Takada[25] used 4 weekly cycle of chemotherapy in concurrent arm. Another reason may be small sample size in our study.

Conclusion:

Tumor response favour early concurrent chemo radiation, however results are not statistically significant but chemo morbidity (significant hematologic and gastrointestinal toxicity) were more in concurrent arm compared to sequential arm.

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