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Original Research Article

A comparative study on concurrent chemoradiation using cisplatin versus carboplatin in the management of locoregionally advanced non-small cell lung cancer

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ABSTRACT

Background: Concurrent chemoradiation is considered the standard care for locoregionally advanced non-small cell lung cancer. This study aimed to compare the treatment response, progression free survival and treatment toxicities between cisplatin and carboplatin based concurrent chemoradiation.
Methods: Between October 2015 and September 2017, 60 eligible patients were enrolled and divided into two arms of 30 patients each. Arm A received EBRT to chest (60Gy/30 fractions) with concurrent weekly Injection Cisplatin 35mg/m2. Arm B received EBRT to chest (60Gy/30 fractions) with concurrent weekly Injection Carboplatin at a dose of AUC-2. Early treatment response was assessed at 1 month and late treatment response at 6 months after completion of radiation using RECIST criteria. Treatment toxicities was assessed using RTOG toxicity criteria. All statistical analysis was carried out using SPSS version 21.
Results: Most patients were in the age range of 61-70 years. Mean age of presentation was 67.53±11.038 years in Arm A and 66.03±12.794 years in Arm B. Median follow up was 16 months for both arms. Response rate of was slightly better in Arm A (73.3% versus 60%). 1 year PFS rate was 53.33% in Arm A and 36.67% in Arm B. Median time to progression was better in Arm A (11 months vs 10 months). Toxicities were almost comparable in both the arms.
Conclusions: Use of carboplatin in combination with radiation therapy is comparable to cisplatin in terms of treatment outcomes with better compliance and lower toxicity.

Keywords: Carboplatin, Cisplatin, Concurrent chemoradiation, Locoregionally advanced non-small cell lung cancer

INTRODUCTION

Lung cancer is one of the most common malignancies world-wide. Among males, lung cancer is the most commonly diagnosed cancer and leading cause of cancer death. Worldwide among females, it is the fourth most commonly diagnosed cancer and the second leading cause of cancer death.[1] The estimated number of lung cancer cases worldwide has increased by 51% since 1985 (a 44% increase in men and a 76% increase in women).[2] Per year, 1.3 million people die of lung cancer which is quite a high number.[3] The major histological types of lung cancer are Small cell lung cancer (SCLC) and Non-small cell lung cancer (NSCLC). NSCLC accounts for about 80% of the total lung cancers and the remaining 20% comprise of SCLC.[4] Non small lung cancer is a term used for a group of cancers originating in the lung that

includes adenocarcinoma (30%- 40%), squamous cell carcinoma (30%), undifferentiated large cell carcinoma (10%) and adenosquamous carcinoma.[5]

The majority of lung cancer cases have been convincingly proven to be associated with smoking. Its incidence and mortality patterns are consistently associated with 20 or more years of smoking history.[6] Inoperable locoregionally advanced lung cancer mainly comprises stage III (TNM classification). In the past, radiotherapy was considered the standard therapy in stage IIIA and IIIB but demonstrated very low survival, poor local control and early development of distant disease. Patients with inoperable stage III disease treated only with thoracic radiotherapy experienced a median survival of 9-11 months, 2-year survival of 10-20% and 3-year survival of 5-10%.[7] There are various therapeutic options for the treatment of locally advanced NSCLC. The choice of which will depend on the patient's clinical situation, closely linked to their performance status, how far advanced the tumor is at diagnosis, and the facilities available at the hospital. For patients with unresectable stage III disease, the standard approach for fit patients is concurrent chemoradiotherapy or sequential chemotherapy and radiotherapy for patients who cannot tolerate the concurrent treatment.

The platinum based combination regimens are considered to be the standard treatment of care for patients with locally advanced NSCLC. Cisplatin based chemoradiotherapy has extensively been investigated in patients with locally advanced non-small cell lung cancer in many randomized trials and is now considered to be the standard treatment.[8] While being one of the most potent chemotherapeutic agents, cisplatin is highly toxic to various organs. Nausea and vomiting are the common toxicities while nephrotoxicity and ototoxicity are some of the most commonly reported serious side effects during cisplatin based chemotherapy. Other side effects, such as hematologic and central nervous system-related toxicities, are often dose limiting factors or reason for treatment interruption. The patient compliance is low due to adverse events.[9] Although weekly Cisplatin is relatively well tolerated, cisplatin's potential nephrotoxicity, highly emetogenic effects, and need for a large amount of hydration could result in hesitation over its use, particularly in patients with renal dysfunction.[10] In the backdrop of the various studies regarding the varying efficacy and the toxicities of various platinum compounds, the purpose of the present study is to compare the treatment response (tumor mass reduction) and toxicity profile in concurrent chemoradiation using cisplatin and carboplatin in the management of advanced inoperable NSCLC.

METHODS

A randomized controlled study was conducted in the Department of Radiation Oncology, RIMS between October 2015 to September 2017. 60 patients of Cytological/histopathologically confirmed inoperable Stage III and stage IVA non-small cell lung carcinoma with Karnofsky Performance Status (KPS) ≥ 60% were included. All the patients were subjected for complete history and thorough general physical examination, complete blood count, blood chemistry, chest X-ray (PA view), ultrasound whole abdomen, pulmonary function test, CT scan thorax, ECG, Urine R/E, blood sugar and other investigations as required. Informed consent was taken for all the patients.

Inclusion criteria

- Cytological/histopathologically confirmed inoperable Stage III and stage IVA non-small cell Lung carcinoma.
- Karnofsky Performance Status (KPS) ≥ 60%
- Hemoglobin ≥10 gm%
- TLC ≥ 4000/mm3
- Platelet count ≥ 100,000/mm3
- Normal Kidney Function Test, Liver Function Test, Blood Sugar
- Age above 30 years and below 70 years
- Normal ECG
- Normal baseline audiometry

Exclusion criteria

- Patient not given consent
- Patients having second malignancy
- Associated major co morbid medical conditions
- Pregnant and lactating women
- Presence of psychosis
- Previously treated with radiation therapy/ chemotherapy and /or surgery

Treatment plan

Control arm (Arm A)

Patients were treated with external beam radiotherapy to the chest to a total dose of 60 Gy delivered in 30 fractions concurrently with weekly administration of injection Cisplatin 35mg/m2/dose for 6 weeks.

Study arm (Arm B)

Patients in this Arm were treated with external beam radiotherapy by the same radiation schedule and dosage as the control arm concurrently with administration of Weekly Injection Carboplatin AUC-2 weekly for six weeks.

Radiation treatment

Both the arms received same radiation regimen. Treatment planning was done in the conventional method by using chest radiographs and contrast enhanced CT of thorax. External beam radiotherapy was delivered using

cobalt-60 teletherapy machine (Theratron 780-C) with a source to skin distance (SSD) of 80cm to a total dose of 60 Gy over 30 fractions (five days in a week). The planned target volume included involved primary lung disease, ipsilateral hilum in N2 and contralateral hilum also for N3, involved lymphatic metastatic disease with a margin of 2cm as based on X-ray/ CT scan findings. Radiation was delivered by two opposing postero-anterior fields. Spinal cord was spared after 46Gy/23 fractions. The remaining radiation dose was given for the reduced field. As per derangement in blood parameters, either blood product transfusions or G-CSF/ GM-CSF were given. Other co-medications and supportive care were allowed.

Follow up and assessment

During the radiation treatment, patients were evaluated weekly for development of any toxicity. Complete haemogram and biochemical parameters were checked before the start of radiation and were done weekly for evaluation of blood counts and biochemical parameters during treatment. The early treatment response was assessed at 1 month following completion of radiotherapy in accordance with RECIST criteria and late response was assessed at 6 months after the completion of treatment. Late toxicities were assessed at 6 months after the treatment in accordance with RTOG criteria. After completion of radiotherapy, the patients were followed up at monthly intervals, till the completion of the study. All statistical analysis was carried out using SPSS 21. A p-value of less than 0.05 was accepted as statistically significant.

RESULTS

Age distribution

It was observed that most of the patients fall in the age range of 61-70 years with 80% in arm A and 80% in arm B and the age distribution among both the Arms are also similar (Figure 1).

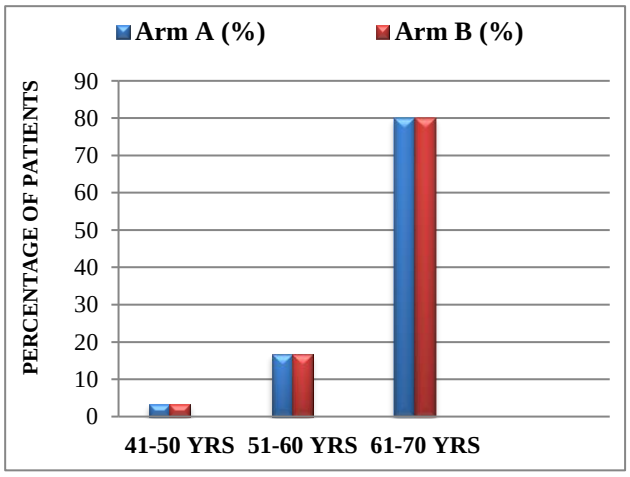


Figure 1: Age group distribution of patients.

Sex distribution

It was observed that out of 30 patients in Arm A, 16 (53.3%) patients were male and 14 (46.7%) patients were female. In Arm B, 17 (56.7%) patients were male and 13 (43.3%) were female. The sex wise distribution among the arms were almost similar (Figure 2).

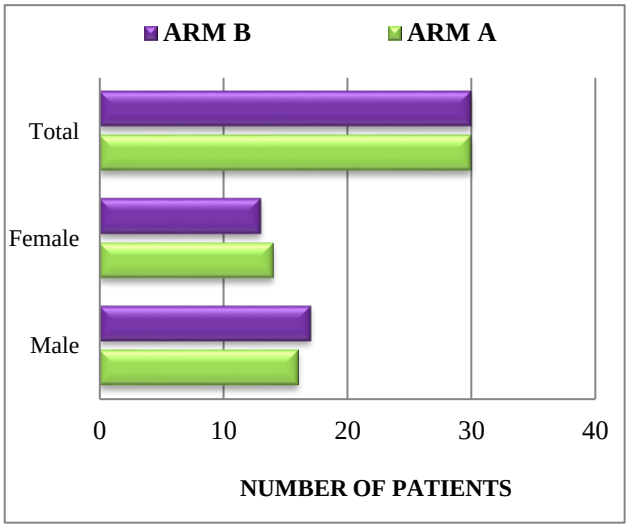
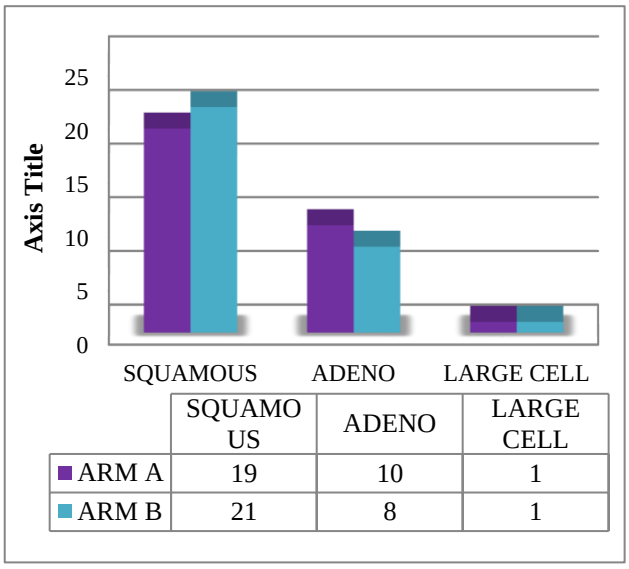


Figure 2: Sex distribution among the two study arms.

Histological types

In Arm A 63.3% were squamous cell and 33.3% adenocarcinoma whereas In Arm B, 70% were Squamous cell carcinoma while 26.67% were adenocarcinoma. A small proportion of the patients were found to be large cell carcinoma accounting for only 3.3% of the patients in each arm.

The distribution of different histologies are almost similar in both Arms (Figure 3).



	SQUAMOUS	ADENO	LARGE CELL
ARM A	19	10	1
ARM B	21	8	1

Figure 3: Histopathological types.

Stage distribution

Table 1 shows the stage wise distribution of the study sample. In stage IIIA, 8.3% of the patients were in Arm A and 15% in Arm B. While in stage IIIB 41.7% and 35% were in Arm A and Arm B respectively. This distribution shows the p-value of 0.360 which is statistically insignificant.

Table 1: Stage distribution.

Stage		Group		p-value
		Arm A	Arm B	
IIIA	$T_1N_2M_0$	1	2	0.360
	$T_2N_2M_0$	2	3	
	$T_3N_2M_0$	2	4	
Total		5 (8.3%)	9 (15%)	
IIIB	$T_4N_2M_0$	9	5	
	$T_1N_3M_0$	3	2	
	$T_2N_3M_0$	5	6	
	$T_3N_3M_0$	3	4	
	$T_4N_3M_0$	5	4	
Total		25 (41.7%)	21 (35%)	
Total		30	30	

Treatment response

Table 2 shows the overall treatment response at the end of 1 month in both the Arms. All the 60 patients (in both arms) were available for assessment at the end of 6 months.

Table 2: Early treatment response at the end of 1 month, arm A vs arm B.

Treatment response	Treatment Arm		p value
	Arm A	Arm B	
CR	2	1	0.700
PR	20 (64%)	17 (72%)	
SD	7 (36%)	10 (28%)	
PD	1	2	
Total	30	30	

Two complete responses and 20 partial responses were obtained with the Cisplatin arm (Arm A). One complete response and 17 partial responses were obtained in the Carboplatin arm (Arm B). The response rates were 73.3% with Arm A and 60% with Arm B (all assessable patients). The differences were not statistically significant (P = 0.70).

On binomial logistic regression analysis, patients in Arm A had more probability of having a tumor response, when compared to Arm B, Hazard ratio 1.833 (95% CI- 0.616-5.453, p-value 0.276). But Arm B had a better percentage of patients having a stable disease. The disease stabilized in seven patients in Arm A and in ten patients in the Arm B. Early progression (during therapy) occurred in 1 patient in treatment Arm A (squamous in histological type) and 2 patients in Arm B (one squamous and one adenocarcinoma type).

Late treatment response and survival

Survival was analyzed after a median follow-up of 17 months. Out of 60 patients evaluated after completion of the treatment.

Table 3: Late treatment response and survival.

	Arm A	Arm B	p value*
Median follow up	16 months	16 months	0.523
Mean PFS	11.2±0.57 months	10.2±0.65 months	
Median PFS	12±1.357 months	11±0.880 months	

Table 3 shows the late treatment response and survival where median follow up was 16 months in arm A and 16 months in arm B with a median progression free survival of 12 months and 11 months in arm A and arm B respectively. p value was 0.505 which was statistically not significant.

The progression-free survival at one year was assessed for 40 patients (20 patients in each arm), since 10 patients were either lost to follow up or expired during the time period.

Progression free survival at one year was found to 53.33% in Arm A and 36.67% in Arm B (log-rank test, p= 0.194). On comparing weekly cisplatin Arm (Arm A) with weekly Carboplatin Arm (Arm B), one-year progression free survival is minimally better for Arm A, even though not statistically significant Hazard Ratio=1.184 (95%CI -0.694-1.923, p- Value-0.516).

Treatment toxicities

Table 4 shows the treatment related toxicity and early side effects which was noted as per RTOG criteria. Early toxicities particularly nausea, vomiting and hematological parameters were assessed after each cycle of chemotherapy. During radiation treatment lung and esophageal toxicity were assessed every week for 6 weeks.

The most common side effects during chemotherapy were nausea (92%) and vomiting (80%) especially during the 1st cycle of chemotherapy and were mostly grade 1.

The side effects of RT were mostly seen in 3rd week after starting of treatment in arm A, grade 1 and grade 2 lung toxicity was found to be 56% and 16% respectively and grade 1 and 2 esophageal toxicity was found to be 52% and 12% respectively.

Table 4: Acute toxicity.

Symptom	Week	Grade	Arm A	Arm B
Cough	Week 3	1	25 (83.3%)	24 (80%)
		2	5 (16.7%)	6 (20%)
		3	1 (3.33%)	0
	Week 4	1	22 (73.33%)	25 (83.33%)
		2	5 (16.67%)	3 (10%)
		3	0	0
	Week 5	1	20 (66.67%)	22 (73.33%)
		2	4 (13.33%)	4 (13.33%)
		3	0	0
	Week 6	1	16 (53.3%)	15 (30%)
		2	2 (6.67%)	3 (10%)
		3	0	0
Oesophagitis	Week 3	1	17 (56.67%)	18 (60%)
		2	3 (10%)	4 (13.33%)
	Week 4	1	19 (63.3%)	20 (66.67%)
		2	8 (26.67%)	8 (26.67%)
	Week 5	1	21 (70%)	20 (66.67%)
		2	5 (16.67%)	5 (16.67%)
	Week 6	1	21 (70%)	20 (66.67%)
		2	12 (40%)	12 (40%)
Nausea	Week 3	1	7 (23.33%)	5 (16.67%)
		2	2 (6.67%)	2 (6.67%)
	Week 4	1	6 (20%)	5 (16.67%)
		2	3 (10%)	4 (13.33%)
	Week 5	1	3 (10%)	2 (6.67%)
		2	1 (3.33%)	1 (3.33%)
	Week 6	1	1 (3.33%)	0
		2	0	0
Vomiting	Week 3	1	4 (13.33%)	3 (10%)
		2	0	0
	Week 6	1	1 (3.33%)	0
		2	0	0
Haemoglobin	Week 3	1	1 (3.33%)	1 (3.33%)
		2	0	0
	Week 4	1	2 (6.67%)	3 (10%)
		2	0	1 (3.33%)
	Week 5	1	2 (6.67%)	3 (10%)
		2	0	2 (6.67%)
	Week 6	1	3 (10%)	5 (16.66%)
		2	0	3 (10%)
TLC	Week 3	1	0	1 (3.33%)
		2	0	0
	Week 4	1	0	2 (6.67%)
		2	0	1 (3.33%)
	Week 5	1	2 (6.67%)	4 (13.33%)
		2	1 (3.33%)	3 (10%)
	Week 6	1	4 (13.33%)	7 (23.33%)
		2	2 (6.67%)	4 (16.67%)
Platelet	Week 3	1	0	2 (3.33%)
		2	0	0
	Week 4	1	1 (3.33%)	2 (3.33%)
		2	0	0
	Week 5	1	2 (6.67%)	3 (10%)
		2	0	0
	Week 6	1	0	3 (10%)
		2	0	1 (3.33%)

Table 5 shows late side effects of the treatment for lungs and esophagus which were assessed in 58 patients each for arm A and arm B at 6 months after completion of treatment. For lungs Grade 1 toxicity was seen in 43.3% and 46.7% in Arm A and Arm B respectively. No grade 4 lung fibrosis was observed. Esophageal toxicity grade 1was seen in only 20% of the patients at 6 months.

Table 5: Late side effects of treatment (assessed at 6 months post treatment).

Adverse effects	Arm A	Arm B
Lung fibrosis		
Grade 1	13 (43.33%)	14 (46.67%)
Grade 2	8 (26.67%)	8 (26.67%)
Grade 3	2 (6.67%)	2
Dysphagia		
Grade 1	6 (20%)	4 (13.33%)
Grade 2	2 (6.67%)	2 (6.67%)
Grade 3	-	-
Myelitis	-	-
Ototoxicity	2 (6.67%)	-
Neurotoxicty	5 (16.67%)	4 (13.33%)

DISCUSSION

Chemoradiotherapy has been established as the standard treatment for patients with inoperable stage III NSCLC. Several trials indicate that concurrent chemoradiotherapy improves long-term survival compared with sequential CRT.[11] Cisplatin remains one of the standard chemotherapy regimens. The efficacy of chemoradiotherapy while using another platinum compound, Carboplatin has also been reported.[12,13] The direct comparison has not been done between these two platinum compounds, when used as a radiosensitiser especially in India.

Non-small cell lung cancer (NSCLC) represents approximately 75 to 80% of lung cancer cases, and often presents at an advanced stage (stage III-IV) that is usually beyond surgical intervention. Treatment of stage III NSCLC remains a very difficult and controversial area mainly because of the large heterogeneity of different pathological conditions. Poor survival with surgery alone has led to an effort to add chemo and/ or radiotherapy to the loco regional treatment. Although a number of significant advances have been made in multimodality treatment of NSCLC, no clearly superior option has emerged for unresectable NSCLC.

The first report on improved 1 and 2-year survival after adding chemotherapy to the irradiation was published by Dillman et al.[14] In 1995, a meta-analysis based on individual data from 3,033 patients showed that combining chemotherapy and radiotherapy gave a statistically significant benefit.[15] This difference was greater in those trials that had used platinum treatment, with a hazard ratio of 0.87 (P<0.005) in favour of combined chemotherapy and radiotherapy treatment.

The Radiotherapy and Lung Cancer Cooperative Groups of the European Organization for Research and Treatment of Cancer (EORTC) had initiated a randomized phase II (preliminary) study to compare radiotherapy alone with radiotherapy plus cisplatin given on the first day of each treatment week, and with radiotherapy preceded daily by cisplatin, in patients with inoperable non-small-cell lung cancer.[16] The hazard ratio resulting from the addition of platin-based concomitant chemotherapy to radiotherapy was 0.89 (95% CI, 0.81 to 0.98), but this had to be interpreted cautiously owing to heterogeneity across trials and sensitivity analyses yielding inconsistent results.[17] Single agent Carboplatin administered weekly was used in only one trial.[18]

In this study most of the patients fall in the age range of 61-70 years with 80% each in both the arms. This follows the general trend that lung cancers occur in older age group patients. The age groups for the patients were also similar among both the study arms. Out of 30 patients in Arm A 53.3% were male and 46.7% female. In Arm B 56.7% and 43.3% of patients are male and female respectively. 56.7% of total patients have KPS of 70% in arm A and arm B.

Mean age of presentation in Arm A is 67.53±11.038 years (Range 31-86 years) and in Arm B is 66.03±12.794 years (Range 45- 86 years). This is in contrast to study done by Patterson CJ et al, where the mean age is 79 years.[19] Similarly, in a study conducted by Fairchild A et al, the numbers of male patients in the study were 78% and the mean age was 63 years with the range of 60 to 67 years.[20]

In the present study 16.7% belong to Stage III A in Arm A and 30% of patients in Arm B. 83.3% and 70 % were found to be in stage IIIB in Arm A and Arm B respectively. In Arm A, 63.3% of the patients were found to have squamous cell carcinoma compared to 70% in Arm B, while 33.3% patients in Arm A were having a histology type of adenocarcinoma compared to 26.7% in Arm B. The distribution of the histopathological types is almost similar in both Arms. The patient characteristics of both groups were well balanced without statistically significant differences in age, stage, KPS and histology although the mean age of Arm A (cisplatin) was slightly higher than Arm B (carboplatin arm) (67.53 years vs. 66.03 years; p = 0.051).

Toxicity profile (Acute toxicities)

During the 6 weeks of treatment course, lung and esophageal toxicities were comparable in both arms of the study. Grade 1 esophageal toxicity was present in 70% of patients in both the arms. The esophageal toxicities increase over the weeks in both arms. A statistically significant difference could not be elicited

among the Arms (p value - 0.77). Nausea and vomiting were more prominent in arm A. Grade 1 nausea and vomiting were 30% and 16.67% respectively, which were seen mostly in 2nd and 3rd week. It has been proven from prior studies that Cisplatin has amore emetic potential when compared to Carboplatin.[21-25] There is also not much weekly variation in the incidence of nausea and vomiting among the two study arms.

Hematological toxicities were noticed to be mildly increasing as the chemotherapy progresses. No grade 2 anaemia was found during 5th and 6th cycle in Arm A whereas in Arm B, grade 2 anemia was found in 7% and 10 % respectively during 5th and 6th weeks respectively. Similarly, leucopenia grade 2 was less in Arm A compared to Arm B during the 5th and 6th weeks. There was not much variation in thrombocytopenia, but Arm A was found to have less incidence of thrombocytopenia events when compared to Arm B (10% in Arm A vs 20% in Arm B). Similar incidence was also seen in studies done by Bhal et al especially the increasing frequency of hematological toxicity from cycle 4-6.[26]

Tumor response rate after the treatment

Two patients in Arm A and one patient in Arm B had complete response as assessed by radiological imaging at one month after the completion of treatment. Disease progression was seen in one patient in Arm A and two patients in Arm B respectively. 64% and 36 % of patients in arm A had partial response and stable disease whereas in arm B, 72% of patient had partial response and 28% of patients had stable disease.

The Hazard ratio of Arm A when compared to Arm B is 1.833 (95% CI- 0.616-5.453), which is significant. But Arm B had a better percentage of patients with stable disease. The response rate achieved in the Arms were similar to the rates achieved in other trials.[27,28] In a study by Schaake Koning et al the response rate achieved while using Weekly cisplatin at 35mg/m2 was found to be 75%. The response rates achieved in the study's both arms are comparable.28

Late response (progression free survival)

In Arm A, 53.33% of patients had a progression free survival at one year compared to 36.67% of the patients in Arm B with a hazard ratio 1.212 (95% CI - 0.555-2.644). Here, it can be seen that there is a difference in the percentage of patients having a progression of disease at one year. The results were comparable to other studies.[29,30]

The median time to progression in Arm A was 11 months and in Arm B was 10 months, but not statistically significant (11 months versus 10 months, p- Value 0.516). These results are comparable to the data published in other studies where the range of progression free survival vary from 9 months to 14 months.[31,32]

Toxicity assessment (Late toxicities)

The incidence of late toxicities in Arm A was used as the radiosensitiser in this study was comparable to the late toxicities noted in Arm B and the incidence of toxicities were in accordance with the findings reported by Trovo et al, Cakir et al, Ichinose et al.[32-34] The incidence of esophageal toxicities in the weekly Carboplatin Arm was also in the range of the values being reported from other similar studies like Groen et al, Vokes et al.[35,36] There was no life threatening toxicities in both arms and all the patients tolerated the treatment well.

In conclusion the use of carboplatin in combination with radiation therapy is comparable to cisplatin in terms of treatment outcomes, even though there is a one month progression free survival advantage in the weekly Cisplatin arm, even though not statistically significant. In addition, the compliance in the carboplatin arm was better and the observed acute toxicity in terms of anemia, and neutropenia was lower in the carboplatin when compared to the cisplatin group. Further studies with larger sample size is required to confirm the finding of the present study.

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