

# Comparison of Induction Chemotherapy with Cisplatin and 5FU Followed by Concurrent Cisplatin with EBRT against Induction Chemotherapy with Paclitaxel and Cisplatin Followed by Concurrent Paclitaxel with EBRT With Regard to Toxicity, Local Control and Overall Survival in Carcinoma Esophagus

Shahida Nasreen<sup>1</sup>, Fir Afroz<sup>2</sup>, Lone M Maqbool<sup>3</sup>, Mansoor ul haq Lone<sup>4</sup>, Ajaz Ahmad Mir<sup>5</sup>, Shahid Wani<sup>4</sup>

## ABSTRACT

**Introduction:** Carcinoma esophagus is a therapeutic challenge. Definitive chemoradiotherapy has a role for patients with locally advanced or unresectable esophageal cancer, and for those patients who are medically unfit for surgery. In light of the activity and improved survival of the Paclitaxel plus Cisplatin regimen in advanced disease and the potent radio sensitising effect of both drugs, this regimen along with radiation has been evaluated in comparison with cisplatin and 5-FU based chemoradiotherapy.

**Materials and methods:** The present prospective, randomised study was carried out directly comparing the outcome of induction chemotherapy with cisplatin and 5FU followed by concurrent cisplatin with EBRT against induction chemotherapy with Paclitaxel and cisplatin followed by concurrent Paclitaxel with EBRT with regard to toxicity, local control and overall survival. Patients aged 50-70yrs with ECOG performance score of 0, 1, 2, locally advanced histologically confirmed SCC of oesophagus were included. Response to treatment was evaluated clinically, on barium swallow and endoscopy with biopsy. Study was conducted at tertiary care hospital, from September 2008 to September 2010.

**Results:** Overall response in Paclitaxel group was higher than cisplatin+5-FU group. These results were statistically significant with p value of 0.003 in favour of Paclitaxel. Overall, survival and disease free survival were better in the Paclitaxel group. The apparent survival benefit and acceptable toxicity profile that we observed emphasizes the importance of a careful prospective investigation of these regimens before their incorporation into standard management.

**Conclusion:** Paclitaxel is a novel agent with radiotherapy in locally advanced SCC of oesophagus with remarkable complete response, improved survival and manageable toxicity.

**Keywords:** Induction chemotherapy, Paclitaxel, Cisplatin, 5FU, concurrent EBRT, carcinoma esophagus.

with locally advanced or unresectable oesophageal cancer, patients who are medically unfit for surgery and for patients refusing surgery. In a series at Fox Chase Cancer Centre, radiotherapy plus chemotherapy consisting of 5-FU and mitomycin produced a local control rate of 75% with improved and an actuarial disease free survival rate in patients having stage I and II disease.<sup>2</sup> Pivotal intergroup randomized trial of chemotherapy plus radiotherapy versus radiotherapy alone resulted in an improvement in the survival rate in the combined modality group.<sup>3</sup> This Trial established a new standard for definitive chemoradiotherapy in patients having loco regional oesophageal carcinoma, particularly squamous cell carcinoma. Furthermore an Eastern Cooperative Oncology Group trial of 135 patients showed that chemotherapy plus radiotherapy provided a better survival rate than did radiotherapy alone.<sup>4</sup>

Recently many studies using concomitant chemoradiotherapy with or without surgery have shown an improvement in local control and survival. In the light of activity and improved survival of the Paclitaxel plus Cisplatin regimen in advanced disease and the potent radio sensitising effect of both drugs<sup>5</sup>, this regimen along with radiation has been evaluated.

The present study was conducted to compare results of induction chemotherapy with cisplatin and 5FU followed by concurrent cisplatin with EBRT against induction chemotherapy with Paclitaxel and cisplatin followed by concurrent Paclitaxel with EBRT with regard to toxicity, local control and overall survival.

## METHODS AND MATERIALS

Patients aged less than 70yrs with ECOG performance score

<sup>1</sup>Attending Consultant, Department of Radiation Oncology, Medanta the Medcity, <sup>2</sup>Professor, <sup>3</sup>Professor and Head, <sup>4</sup>Senior Resident, Department of Radiation Oncology, <sup>5</sup>Resident, Department of Cardiology, SKIMS, Srinagar, Kashmir, India

**Corresponding author:** Mansoor UL haq Lone, C/O Married Doctors Hostel, B-Block, Room G-11, SKIMS, Soura Srinagar, India

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## INTRODUCTION

Carcinoma esophagus continues to be one of the greatest therapeutic challenges. Management of carcinoma esophagus is based on tumour extent according to TNM classification. The treatment is divided into curative and palliative intended treatment. Patients with loco-regional disease (stage I-II), in good medical condition, are offered curative treatment. Patients with nodal metastasis do poorly when treated with surgery alone, with a 5-year survival of less than 20%.<sup>1</sup> Definitive chemoradiotherapy has a role for patients

of 0, 1, 2, having locally advanced histologically confirmed SCC of oesophagus were included (table 1). All patients had adequate renal and hepatic functions. Institutional review board approved the proposal (Research and Ethical Committee). A detailed explanation of the trial was given to patients before obtaining written consent for participation in the trial.

### Pre-treatment staging evaluation

All patients were evaluated with history and examination, CBC, Renal and Hepatic function, Chest x-ray, ECG, Barium esophagogram, EGD with biopsy, CECT chest and upper abdomen, USG abdomen, Bone scan [wherever indicated], Cardiology clearance for chemotherapy.

**Radiation therapy:** After simulation, external beam radiotherapy (EBRT) was delivered with telecobalt unit (Theraton 780E). The patients received a total dose of 65 Gy over a period of six weeks with five fractions per week. Primary treatment of 40 Gy/20# was followed by supplementary treatment of 25 Gy/10#. Primary treatment consisted of two AP/PA portals while the supplementary treatment was carried out by three portals i.e. one anterior and two posterior obliques to exclude the spinal cord. Target volume consisted of 5cm proximal and distal margin beyond primary tumor, 2.5 cm radial margin, and regional nodes (as assessed by barium swallow, EGD findings and CT imaging)

**Chemotherapy:** Dexamethasone with adequate anti emetics were started before the start of chemotherapy along with adequate hydration.

Group I received Cisplatin 75mg/m<sup>2</sup> IV over three hours on day one and 5-FU 1000mg/m<sup>2</sup> per day by continuous infusion over twenty four hours through day one to day four. The cycle was repeated after twenty one days. After three weeks of second cycle concurrent chemoradiation was started in the form of external beam radiation to a dose of 65Gy/30#s. Cisplatin 25mg/m<sup>2</sup> was given Monday of every week during radiation therapy. Group II received Paclitaxel 175mg/m<sup>2</sup> IV infusion over 24hours on day one and Cisplatin 75mg/m<sup>2</sup> IV over three hours on day two. Second cycle was repeated after 21days. After three weeks of second cycle concurrent chemoradiation was started in the form of external beam radiation to a dose of 65GY/30#s. Paclitaxel 30mg/m<sup>2</sup> was given on day first of every week during radiation therapy.

**Assessment of toxicity:** Toxicity was assessed weekly during treatment and thereafter monthly up to three months for acute toxicity using RTOG criteria. Then the patients were followed monthly for six months, then three monthly for any signs of local recurrence and treatment related morbidity. Acute side effects were defined as those occurring within ninety days and late side effects as those occurring after ninety days

**Study Design:** This prospective, randomised study, directly compared the outcome of induction chemotherapy with cisplatin and 5FU followed by concurrent cisplatin with EBRT against induction chemotherapy with Paclitaxel and cisplatin followed by concurrent Paclitaxel with EBRT. Study was conducted at Sheri-I-Kashmir Institute of Medical Sciences Srinagar, from September 2008 to September 2010. All eligible patients were registered and provided written informed consent before entry into the trial. The primary study end-

point was response assessment, overall survival, and secondary endpoints were failure pattern, acute and late toxicity. The statistical analysis of the data was done by the chi-square test and in quantitative data analysis mean± standard deviation (mean±S.D.) was found. The significance was checked using p-value and p-value less than 0.05(p<0.05) was taken to be statistically significant. Survival curves were constructed using the Kaplan-Meier method and compared using the log-rank test. All statistical analysis were performed using statistical package SPSS, version 11.5(Chicago, Illinois).

**Endpoint assessment and follow up:** A complete response (CR) for the primary tumor was defined by endoscopy when all visible tumors, including ulcerations, disappeared and the result of the biopsy proved negative. Response of metastatic lymph nodes were assessed by CT scans by use of the WHO response criteria for measurable diseases. Each group was evaluated at the end of each treatment cycle, every 3 months for 2 years, and every 6 months for the next 3 years.

## RESULTS

A total of 68 patients with previously untreated locally advanced esophageal squamous cell carcinoma were enrolled in the study. Out of these 8 were excluded because of the following reasons, One patient was detected with second malignancy after first cycle of chemotherapy, 3 patients deteriorated and developed low performance score during pre-treatment evaluation patients, 2 had tracheoesophageal fistula when investigated, 2 refused to continue treatment after first cycle. Therefore, a total of 60 patients were available for the inclusion, of which 30 were randomised to receive Cisplatin + 5-FU chemotherapy (Group I) while 30 received Cisplatin + Paclitaxel chemotherapy (Group II). Patient characteristics are listed in table 1. The potential prognostic factors for survival were well balanced between the randomised groups.

**Toxicity:** Toxicity related to chemoradiation is listed in table 2. Group II patients developed more myelosuppression but group I patients had more GI and cardiac toxicity.

**Survival:** Of the total of 60 patients, 16 either died or were lost to follow up. The remaining 44 (73.33%) patients were followed up for survival analysis over the rest of the period of study. The survival probability estimates were obtained by the Kaplan-Meier method. The median follow up was 15 months (range 9-25 months). The median survival time of patients in Group I was 16 months (range 9-25 months and 95% Confidence Interval, 15-17); whereas in Group II, the median survival time was 18 months (range 12-25 months and 95% Confidence Interval, 16-20). This difference in survival in two groups was statistically significant with p=0.003 as shown in table 3.

## DISCUSSION

Many treatment modalities are being tried to improve survival in locally advanced SCC of esophagus. Paclitaxel enhances the effect of radiation by synchronisation of cell cycle at the most sensitive phase (G2/M). Cisplatin enhances radiosensitivity by inhibition of radiation induced DNA repair. We tried to incorporate these drugs with radiation therapy and assess toxicity and disease free and over-all response.

Apart from acute gastrointestinal toxicity, myelosuppression and bradycardia were the most common treatment related toxicities being statistically significant in paclitaxel-cisplatin group (Group-II) 73.33% patients in this group developed leucopenia with around 46.66% patients having grade 3-4 toxicity. Neutropenia was observed in 60% patients in Group I, of which 3 patients developed grade-4 toxicity. These toxicities were manageable with only 3 (10%) patients requiring hospital based management and G-CSF support. No patient expired because of toxicity. This toxicity although less, was comparable to that in a study by Ilson DH et al<sup>6</sup> who conducted a phase trial of cisplatin-paclitaxel in 38 patients with carcinoma esophagus, and observed 47% cases of grade 3-4

neutropenia. In this study, 19 (50%) patients required hospitalization and 4 patients (11%) died from therapy related complications, predominantly myelotoxicity. Hematological toxicity in our study was also better than those observed by Aldestein et al<sup>7</sup> who reported >3 neutropenia in 95% of the studied population. Meluch AA et al.<sup>8</sup> also reported almost similar hematological as our study with leukopenia of 65%, however, C-Clin et al.<sup>9</sup> reported less haematological toxicities than our study. They reported grade 3 or 4 leukopenia in 30% and 16% of patients, respectively. 11% and 10% of patients have grade 3 or 4 anaemia and thrombocytopenia. In our study, Paclitaxel based regimen (Group-II) produced less gastrointestinal toxicity although not statistically significant. Forastiere and associates<sup>10</sup> have also reported significant gastrointestinal toxicity with 5-FU+Cisplatin chemoradiation with most patients requiring nutritional support in their study, and suggested to look for alternatives to 5-FU based chemotherapy. In the most widely used regimens for chemoradiotherapy for localized esophageal carcinoma, the RTOG 85-01 trial.<sup>3</sup> Chemoradiotherapy with cisplatin/5-FU was associated with 44% and 20% grade 3 and 4 acute toxicities, primarily gastrointestinal. Heath et al (128) reported similar results with 5-FU/Cisplatin combination therapy. In this regard, our results are encouraging considering the manageable myelotoxicity and decreased gastrointestinal toxicity in Group-II patients (Paclitaxel based). Non haematological complications like neuropathy, radiation toxicity of skin were equal in both groups. However bradyarrhythmias were more common in Group I patients, as it is already known to occur in patients on infusional 5-FU<sup>8</sup>, occurred in 6 (20%) patients in Group-I. Our overall response in paclitaxel group was 93.33%. 28 patients have an overall response with 9 (30%) patients achieving complete response and 19 (63.33%) achieving partial response. Response to treatment was evaluated clinically, on barium swallow and endoscopy with biopsy. In cisplatin+5-FU group 23 (76.66%) patients achieved overall response with only one (3.33%) patient having a complete response. These results were statistically significant with p value of 0.003 in favour of Paclitaxel. But more evidence needs to be provided in this regard with a longer study group involving more number of patients. On comparing with a similar cohort of patients treated with cisplatin/5-FU based regimen, there was suggestion of a superior outcome from the substitution of paclitaxel. Overall survival and disease free survival were better in the paclitaxel group. The median survival in this group was 18 months as compared to 16 months in 5-FU based regimen, the difference being statistically significant. However, no statistically significant difference could be achieved in the final outcome between the two treatment regimens. The inference is clearly difficult to make due to small population size, even the two cohorts were well matched. Recently, promising results from several phase II paclitaxel based chemoradiotherapy trials in esophageal cancer have been reported.<sup>11-13</sup> Susan G.UR-

	Group I	Group II
Total no. Of patients	30	30
Age in years		
Mean	59	58
Range	48-70	45-70
Male/Female	18/12	17/13
Histology	SCC	SCC
Tumor size		
<5cm	10	11
>5cm	20	20
Tumor site		
upper 1/3 <sup>rd</sup> (25cm)	2	3
Middle 1/3 <sup>rd</sup> (25-35cm)	21	24
Lower 1/3 <sup>rd</sup> (>35cm)	7	3
LAP on CT		
Yes	22	23
NO	8	7
Dysphagia		
Grade I	13	11
Grade II	14	15
Grade II	3	4

**Table-1:** Patient characteristics:

	Group I	Group II
Leucopenia		
Grade I-II	12	13
Grade III-IV	1	9
Thrombocytopenia		
Grade I-II	17	14
Grade III-IV	0	8
Neutropenia		
Grade I-II	13	10
Grade III-IV	5	12
Vomiting		
Grade II-III	5	2
Diarrhoea		
Grade II-III	14	5
Bradycardia	6	0
Tachycardia	1	0
Sensory Neuropathy	8	13

**Table-2:** Toxicity related to chemoradiation

	Group I	Group II	P value
Median (95% CI)	16 (15, 17)	18 (16,20)	0.018 (sig)
Survival time (months)	14.9±3.7(9,25)	17.8±(12,25)	0.003 (sig)

**Table-3:** Statistically significant difference in survival in two groups with p=0.003

	Group I	Group II
Disease free	1	9
Loco-regional progression	3	2
Distant Failure	6	3
Persistent Local disease	12	8

**Table-4:** Disease status at last follow up

ba et al.<sup>14</sup> in a similar study reported an overall response of 90% with complete response of 27.53%. Orditura et al.<sup>15</sup> also reported similar results with paclitaxel based regimen i.e. overall response 90.90%, partial response 60.60%, and complete response of 30.30% which is almost equal to our study. Melvyn Goldberger et al.<sup>16</sup> in a Paclitaxel based chemoradiotherapy also reported similar results, with overall response of 82%, complete response of 15%, and partial response of 67%. Ferdinando De Vita et al.<sup>17</sup> in a similar study also reported almost equal results, overall response 82%, partial response 49% and complete response 33.3%. However, Huang et al.<sup>18</sup> in a similar study reported lower response rate than our study, they reported, overall survival of 59.3% with partial response of 40.7% and complete response of 18.5% with Paclitaxel based chemotherapy. The apparent survival benefit and acceptable toxicity profile that we observed emphasizes the importance of a careful prospective investigation of these regimens before their incorporation into standard management. Careful clinical staging before treatment will also be crucial for an accurate interpretation of these trials.

## CONCLUSION

Paclitaxel is a novel agent with radiotherapy in locally advanced SCC of oesophagus with remarkable complete response, improved survival and manageable toxicity.

## ABBREVIATIONS

EBRT: External Beam Radiotherapy; 5-FU: 5fluorouracil; ECOG: Eastern Cooperative Oncology Group; SCC: Squamous cell carcinoma; Gy: Gray; #: Fraction; AP/PA: Anteroposterior/posterioanterior; EGD: Esophagogastroduodenoscopy; CT: Computerised tomography; IV: intravenous; m<sup>2</sup>: meter square; RTOG: Radiation therapy oncology group; S.D: standard deviation.

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