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COMPARISON OF SURVIVAL AND ADVERSE EFFECT PROFILE IN PATIENTS WITH ESOPHAGEAL CANCER TREATED WITH THE COMBINATION OF CARBOPLATIN AND PACLITAXEL *VS.* 5-FLOUROURACIL AND CISPLATIN

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Abstract – *Objective:* *Esophageal cancer (EC) is a form of gastrointestinal cancer with the worst malignant potential and poor prognosis. This study sought to compare the survival and adverse effect profile in patients with EC treated with Carboplatin and Paclitaxel or 5-Fluorouracil (5-FU) and Cisplatin regimen.*

Patients and Methods: *The study was conducted at the Regional Cancer Centre (RCC), Sher-i-Kashmir Institute of Medical Sciences (SKIMS), Soura, Srinagar, J&K, India for a period of 7 months. A total of 251 patients were included in this retrospective study, of which 177 (Group I) had been treated with the combination of Carboplatin and Paclitaxel while 74 patients (Group II) had been treated with 5-FU and Cisplatin combination.*

Results: *The median overall survival (OS) was 20.7 months for patients in Group I and 17.1 months for patients in Group II (HR: 1.200; 95% Confidence Interval [CI],* p*=0.176). The median progression-free survival (PFS) was 12.26 months for subjects of Group I and 12.33 months for Group II subjects (HR: 0.609; 95% CI;* p*=0.909). Haematological toxicity (≥ grade III) in terms of anaemia, leukocytopenia and thrombocytopenia in Carboplatin and Paclitaxel group (1.7%, 8%, and 18%) was significantly higher than in the 5-FU and Cisplatin group (1.36%, 0%, and 38%) (95% CI;* p*<0.05). Among non-haematological toxicities, bradycardia was the most notable side-effect of 5-FU and Cisplatin group (18.9%) followed by diarrhoea/vomiting (6.75%) and cough (2.7%). The major side-effect seen in patients treated with the combination of Carboplatin and Paclitaxel was diarrhoea/vomiting (4.52%), followed by mucositis (3.39%) and cough (2.25%) (95% CI; p<0.05).*

Conclusions: *Results suggest that Carboplatin and Paclitaxel regimen is the preferred regimen for patients with potentially curable EC and has higher patient compliance compared to 5-FU and Cisplatin regimen. Toxicity, excluding haematological events, occurred less frequently in the group that received Carboplatin and Paclitaxel compared to toxicity rates in patients who received 5-FU and Cisplatin regimen.*

KEYWORDS: *Esophageal cancer, Carboplatin, Paclitaxel, Cisplatin, 5-FU, survival.*

INTRODUCTION

Esophageal cancer (EC) can occur anywhere along the lining of the esophagus and is considered to be a serious malignancy with respect to prognosis and mortality rate[1]. It is the seventh most common cancer and the sixth most common cause of cancer-related deaths worldwide[2] with developing nations making up more than 80% of total cases and deaths[3]. Both the incidence rate as well as the mortality rate is higher in Asia than in other parts of the world. In 2020, an estimated 604127

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(3.1%) new cases of EC were reported worldwide of which 481552 (79.7%) were from Asia only. Similarly, among 544076 (5.5%) of total cancer-related deaths due to EC, 434363 (79.8%) were reported from Asia[4]. Esophageal squamous cell carcinoma (ESCC) is the most prevalent histological type worldwide, whereas esophageal adenocarcinoma (EAC) is the prevalent type in United States (US) and other Western countries[5]. Worldwide, 60-70% of esophageal cancers are squamous cell carcinomas and about 20-30% are adenocarcinomas[6]. EC is an aggressive cancer with high mortality and an average 5-year survival of 20% [2]. However, 5-year survival rates are increased between 25% and 39% in patients treated surgically with curative intent[7].

Several chemotherapy regimens are currently being used as a definitive regimen in EC patients. The most commonly used regimens are those consisting of a Platinum compound in combination with Pyrimidine antagonist and/ or Taxol based compound. The present study was undertaken to compare the survival and the adverse-effect profile of EC patients treated with the combination of Carboplatin and Paclitaxel against 5-FU and Cisplatin.

PATIENTS AND METHODS

Patients

This retrospective study involving patients with EC was carried out at the Regional Cancer Centre (RCC) of Sher-i-Kashmir Institute of Medical Sciences (SKIMS) Soura, Srinagar, J&K, India – a tertiary care hospital, for a period of 7 months from June 2017 to January 2018. A total of 251 histopathologically confirmed cases, both male and female below the age of 70 years, of EC were included in the study. Patients were included on the basis of clinical confirmation, normal organ (hepatic and renal) function, Eastern Cooperative Oncology Group (ECOG) status ranging from 0-2 and age above 18 years.

Ethical clearance of the study was obtained from the Institutional Ethics Committee (IEC) of the hospital. The authorization certificate for accessing patient record files was also obtained from RCC SKIMS.

Methods

Pre-treatment evaluation

The primary diagnostic tests performed in patients were Barium Swallow and Esophagogastroduodenoscopy (EGD) followed by the biopsy. The patients had also undergone Computed Tomography (CT) evaluation to detect the disease progression.

Treatment regimens

The patients included in the study were divided into two groups on the basis of treatment therapy received for the disease.

Group I

It included the patients who had received Carboplatin in combination with Paclitaxel protocol with or without radiotherapy. The patients had received treatment protocol either as dose 1 (Carboplatin-AUC2 and Paclitaxel 50 mg/m^2 I.V.) or dose 2 (Carboplatin-AUC5 and Paclitaxel 175 mg/m^2 I.V.). Both Carboplatin as well as Paclitaxel were administered as continuous infusions in a single day. In patients, who received dose 1 of Carboplatin-Paclitaxel, the chemo cycles were repeated after every week whereas, in patients receiving dose 2, the cycle was repeated after every 21 days.

Group II

It included patients who had received 5-FU along with Cisplatin protocol with or without radiotherapy. The patients in this group had also received the chemo drugs either as dose 1 (5-FU-750 mg/m^2 and Cisplatin-50 mg/m^2 I.V.) or dose 2 (5-FU-1000 mg/m^2 and Cisplatin 75 mg/m^2 I.V.). Cisplatin was administered I.V. over 3 hours on day 1 and 5-FU I.V. per day over 24 hours through day 1-4. The cycle was repeated after every 21 days.

The patients who had decreased blood counts were advised to go for Granulocyte-colony stimulating factor (GCSF) (FILGRASTIM). Patients in both groups had undergone baseline investigations before receiving each chemotherapy cycle and only those patients, who had normal liver, haematological and renal functions, received chemotherapy. However, in patients who had altered renal functions, the chemo dose was reduced accordingly. Patients who had low blood counts (grade III anaemia, grade III leukocytopenia) were deferred for further chemo cycles until normal counts were observed. The patients in both the groups were administered Dexamethasone and adequate anti-emetics along with adequate hydration before the start of each chemotherapy cycle.

Radiation scheme

The radiotherapy was inducted concurrently with chemotherapy. The External Beam Radiation Therapy (EBRT) planning was carried out after direct simulation on CT. A total radiation dose of 45-65 Gy (median dose 50.4 Gy) was given in daily fractions of 1.6-2 Gy. Primary treatment of 40 Gy & 5# per week for four weeks and was followed by supplementary treatment of 10.4 Gy & 5# per week. Primary treatment consisted of two AP&PA portals while the supplementary was carried out by 3 portals, one anterior and two posterior obliques to exclude the spinal cord.

Outcome

The end-point was taken as the date of death reported or the end of the study (censored). Overall survival was defined as the time interval between the date of diagnosis and the date of death. Progression-free survival was determined from the date of diagnosis to the date of first recurrence or death of any cause.

Data acquisition

The data was collected from the medical records of patients registered at RCC of SKIMS. The patient characteristics included age, sex, type of histopathology, site of involvement, size of the tumour, dysphagia, weight loss, ECOG performance status, mode of treatment, drug dosage and with the number of chemo doses administered with radiotherapy (whether or not the patient was given radiotherapy) and so on. As the dataset was obtained by reviewing medical records of the patient, participant consent was not required as per the guidelines of IEC, although it was confirmed that all patients had signed written informed consent before undergoing the treatment.

Adverse effects

The adverse effects, both immediate and delayed, experienced by patients were measured according to the Common Terminology Criteria for Adverse Events (CTCAE v5.0).

Statistical analysis

The statistical analysis was carried out by using Chi-square test and in quantitative data analysis, Mean ± Standard Deviation (mean ± SD) was found. The significance was checked using *p*-value and p-value <0.05 was considered statistically significant. The overall survival and progression-free survival rates were calculated according to the Kaplan-Meier method and compared using the log-rank test. The patient characteristics and toxicity rates were determined and compared using the Student's *t*-test.

RESULTS

A total of 1859 patients with EC were registered in the cancer registry from January 2011 – December 2015, of which 251 (13.5%) fulfilled the inclusion-exclusion criteria and thus were included in the study (Figure 1). The study included 146 males (58.2%) and 105 females (41.8%). The medi-

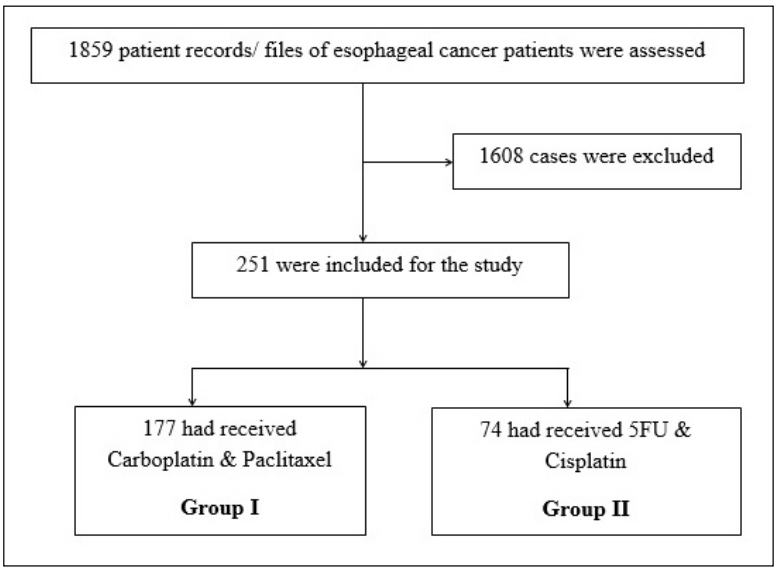

Fig. 1. Flow chart of patients included m the study along with details of different chemotherapeutic regimens received.

TABLE 1. Basic demographic and clinical characteristics of study population.

Characteristic parameter	*Chemotherapeutic Regimen*		*p-value*
	Carboplatin/ Paclitaxel N (%)	*5-FU/Cisplatin N (%)*	
Gender			<0.05
Male	95 (37.8)	51 (68.9)	
Female	82 (46.3)	23 (31.08)	
Age (years)			0.352
≤30	1 (0.5)	0 (0)	
31 - 40	13 (7.34)	7 (9.4)	
41 - 50	25 (14.1)	16 (21.6)	
51 - 60	65 (36.7)	29 (39.1)	
61+	73 (41.2)	22 (29.7)	
Chief Complaint			0.688
Dysphagia only	134 (75.7)	55 (74.3)	
Vomiting	15 (8.47)	4 (5.4)	
Epigastric pain	25 (14.1)	14 (18.9)	
Odynophagia	3 (1.6)	1 (1.3)	
Weight Loss			0.550
No weight loss	128 (72.3)	52 (70.2)	
<10%	37 (20.9)	14 (18.9)	
>10%	12 (6.77)	8 (10.8)	
ECOG Status			0.114
0	5 (2.82)	4 (5.4)	
1	138 (77.9)	63 (85.1)	
2	34 (19.2)	7 (9.45)	
EGD status			<0.05
Lesion up to 25 cm	33 (18.6)	12 (16.2)	
Lesion at 25-35 cm	128 (72.3)	47 (63.5)	
Lesion at above 35 cm	16 (9.03)	15 (20.2)	
Histopathological Evaluation			0.957
Squamous cell carcinoma	172 (97.1)	72 (97.2)	
Adenocarcinoma	5 (2.82)	2 (2.7)	
Site of Involvement			0.087
Upper esophagus	33 (18.6)	13 (17.5)	
Middle esophagus	128 (72.3)	47 (63.5)	
Lower esophagus	16 (9.03)	14 (18.9)	
Size of tumor			0.455
<5 cm	77 (43.5)	36 (48.6)	
≥5 cm	100 (56.4)	38 (51.3)	

an age of the cohort was 60, and the mean age was 57.69 years. The majority of the patients (58.1%) were male with females constituting 41.8% of all patients. The choice of chemotherapeutic regimen for a particular patient was decided on the basis of associated comorbidities and the majority of patients (70.5%) received Carboplatin and Paclitaxel regimen. All patients had received concurrent radiotherapy. Basic demographic characteristics of the patients are listed in Table 1. In Carboplatin and Paclitaxel group 71 patients (40.1%) received 5 cycles of treatment protocol while in 5-FU and Cisplatin group 46 patients (62.1%) had received only 2 cycles of chemotherapy. In Carboplatin and Paclitaxel group the number of chemo cycles given has gone beyond 7 up to 12 in one patient whereas in case of 5-FU and Cisplatin group it has stopped at 6 cycles only (Table 2).

The haematological and non-haematological toxicities associated with each chemotherapeutic regimen are given in Table 3 and Table 4. Among non-haematological toxicities, bradycardia was the most notable side-effect of 5-FU and Cisplatin group and was experienced by 18.9% of patients followed by diarrhoea/vomiting (6.75%) and cough (2.7%) ($p<0.05$; 95% CI). The major side-effect of the Carboplatin and Paclitaxel group was diarrhoea/vomiting, experienced by 4.52% of patients, followed by mucositis (3.39%) and cough (2.25%) ($p<0.05$; 95% CI).

TABLE 2. The number of treatment cycles received by patients with esophageal cancer.

Number of treatment cycles received	*Chemotherapeutic Regimen*		*p-value <0.05*
	Carboplatin & Paclitaxel N (%)	*5-FU & Cisplatin N (%)*	
2 cycles	10 (5.6)	46 (62.1)	
3 cycles	18 (10.1)	11 (14.9)	
4 cycles	37 (20.9)	10 (13)	
5 cycles	71 (40.1)	3 (4.0)	
6 cycles	24 (13.5)	4 (5.4)	
≥7 cycles	17 (10)	0 (0.0)	
Total	177 (70.5)	74 (29.5)	

TABLE 3. Non-hematologic toxicity profile of patients with esophageal cancer.

Non-hematological toxicities	*Chemotherapeutic Regimen*		*p-value <0.05*
	Carboplatin & Paclitaxel N (%)	*5-FU & Cisplatin N (%)*	
None	157 (88.7)	51 (68.9)	
Bradycardia	0 (0.0)	14 (18.9)	
Diarrhea + vomiting	8 (4.52)	5 (6.75)	
Chemo induced mucositis	6 (3.39)	0 (0.0)	
Cough with expectoration	4 (2.25)	2 (2.70)	
Aspiration pneumonia	0 (0.0)	1 (1.36)	
Coronary spasm	2 (1.13)	1 (1.36)	
Total	177 (70.5)	74 (29.5)	

TABLE 4. Hematological toxicity profile of patients with esophageal cancer.

Hematological toxicities[†]	*Chemotherapeutic Regimen*		*p-value <0.05*
	Carboplatin & Paclitaxel N (%)	*5-FU & Cisplatin N (%)*	
Anemia			
Normal	69 (38.9)	38 (51.3%)	
Grade I	70 (39.5)	27 (36.5%)	
Grade II	35 (19.8)	8 (10.9%)	
Grade III	3 (1.7)	1 (1.36%)	<0.05
Grade IV	0 (0.0)	0 (0.0%)	
Total	177 (70.5)	74 (29.5%)	
Leukocytopenia			
Normal	57 (22.7)	54 (21.5)	
Grade I	44 (17.5)	13 (5.2)	
Grade II	56 (22.3)	7 (2.8)	
Grade III	20 (8.0)	0 (0)	<0.01
Grade IV	0 (0)	0 (0)	
Total	177 (70.5%)	74 (29.5%)	
Thrombocytopenia			
Normal	80 (45.2)	50 (67.5)	
Grade I	79 (44.7)	23 (31.0)	
Grade II	16 (9.03)	0 (0.0)	
Grade III	2 (1.13)	1 (1.36)	<0.01
Grade IV	0 (0.0)	0 (0.0)	
Total	177 (70.5)	74 (29.5)	

(CTCAE version 5.0).

[†]Grading was done according to the Common Terminology Criteria for Adverse Events.

The overall haematological parameters were significantly deranged in Carboplatin and Paclitaxel group. The anaemia grade I, II, III, IV was observed in 39.5, 19.8, 1.7% and 0.0% of patients treated with Carboplatin and Paclitaxel respectively (p<0.05; 95% CI). On contrary, anaemia grade I, II, III, and IV was seen in 36.5, 10.9, 1.36 and 0.0% of patients treated with 5-FU and Cisplatin respectively (p<0.05; 95% CI). Leukocytopenia grade I, II, III, IV was observed in 17.5, 22.3, 8, and 0% of patients treated with Carboplatin and Paclitaxel respectively whereas in 5-FU and Cisplatin group it was noted to be 5.2, 2.8, 0 and 0% respectively (p<0.001; 95% CI).Grade I, II, III, IV thrombocytopenia was 44.7, 9.03, 1.13, and 0% respectively in Carboplatin and Paclitaxel group against 31, 0, 1.36 and 0% respectively in 5-FU and Cisplatin group (p <0.05; 95% CI).

The median overall survival (OS) was 20.7 months for patients treated with Carboplatin and Paclitaxel and 17.1 months for patients treated with 5-FU and Cisplatin (Table 5; Figure 2). The mean OS was 29.1 months for patients treated with Carboplatin and Paclitaxel and 26.8 months for patients treated with 5-FU and Cisplatin [hazard ratio (HR): 1.200 (0.867 - 1.667); 95% Confidence Interval (CI); p>0.05]. The median progression-free survival (PFS) was 12.26 months for patients treated with Carboplatin and Paclitaxel and 12.33 months for patients treated with 5-FU and Cisplatin (Table 5; Figure 3). The mean PFS was 14.70 months for patients treated with Carboplatin and Paclitaxel and 14.75 months for patients treated with 5-FU and Cisplatin [HR: 0.609 (0.375 to 0.990); 95% CI, p>0.05).

DISCUSSION

Currently, the most widely used chemotherapeutic regimens are based on a Platinum compound in combination with 5-FU and/or Taxol. The primary objective of this study was to compare the survival and adverse effect profile of patients with EC receiving either Carboplatin and Paclitaxel or 5-FU and Cisplatin treatment as a standard therapy. In this retrospective study of 251 patients suffering from EC who underwent chemotherapy, several predictors of OS and PFS were found. These included baseline patient factors, treatment factors, and factors related to treatment toxicity and response.

The majority of the patients in this study were above 60 years of age in both sexes, with males outnumbering females in all age groups. This has been confirmed by previous studies where the incidence of EC has been found to be predominant in the elderly population particularly above the age of 60 years [8-10]. Also, the male population has been reported to be affected more than the female population having a ratio of about 2:1 [11,12]. In this study, the majority of patients (85.3%) presented with chief complaints of grade I dysphagia, followed by epigastric pain, vomiting, and odynophagia at the time of diagnosis of the disease (Table 1). This aligns with previous studies which have reported dysphagia to be the foremost and predominant presenting symptom of EC [13-15]. Nearly one-third of the patients did not complain of any loss in body weight at the initial diagnosis of the disease while 20.3% of patients complained <10% loss of body weight. This is in line with various studies reporting that EC is consistently associated with weight loss in nearly half of patients [16,17]. Only 8% of patients presented with ≥10% loss of body weight in the last 6 months which is attributed to the difficulty in swallowing, decreased appetite and increased metabolism from the cancer [16]. The ECOG status of majority of the patients was grade 1 i.e., the patients were ambulatory but had restricted physical activity. About two-third of patients had lesion at 25-35 cm at the time of diagnosis of disease depicting that the involvement of middle esophagus more than upper and lower esophagus. In our study the majority of patients (97.2%) had ESCC. Globally, ESCC remains the predominant histological subtype, as 80% of ECs occur in developing countries where

TABLE 5. Survival parameters in patients with esophageal cancer.

Overall Survival Treatment Group	*Mean (months) (95% CI)*	*Median (months)*
Carboplatin + Paclitaxel	29.1	20.7
5FU + Cisplatin	26.8	17.1
***p*=0.249; Hazard Ratio = 1.200 (0.867 - 1.667) [95%CI]**		
Progression-free Survival		
Carboplatin + Paclitaxel	14.70	12.26
5FU + Cisplatin	14.75	12.33
***p*=0.047; Hazard Ratio = 0.609 (0.375 to 0.990) [95%CI]**		

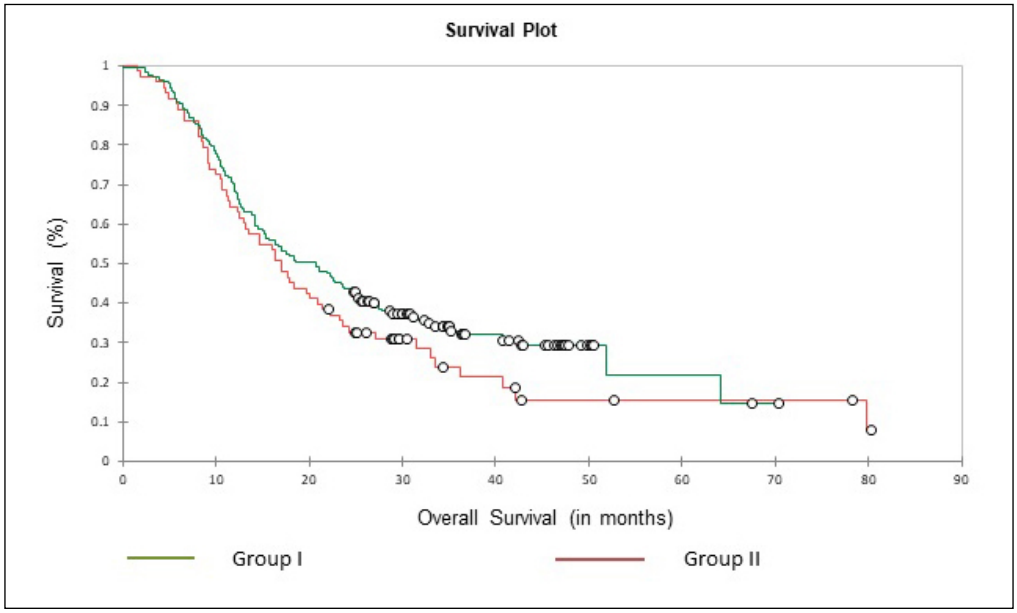

Fig. 2. The Kaplan-Meier overall survival estimates for Group I (Carboplatin & Paclitaxel) and Group II (5FU & Cisplatin) treated patients with esophageal cancer (p=0.176).

ESCC is more common [11,18]. A higher percentage of patients treated with Carboplatin and Paclitaxel completed their treatment compared with the 5-FU and Cisplatin group which depicts that the former protocol has higher patient compliance than the latter.

The non-haematological toxicity profile of the two treatment groups suggests that the overall side-effects of Carboplatin and Paclitaxel group is less compared to 5-FU and Cisplatin. Bradycardia was the most significant side-effect of the 5-FU and Cisplatin group (p<0.05). Haematological toxicities (≥Grade III) were significantly higher in the Carboplatin and Paclitaxel group (p<0.05). Similar to our results, two other studies reported significantly higher toxicity rates for the Paclitaxel regimen [17,19] whereas other studies observed a marginally lower toxicity rate for the Paclitaxel regimen [20,21].

In this study, no significant difference was found in terms of OS and PFS between the two treatment regimens. A similar study conducted by Honing et al [22] reported no significant difference in terms of OS and PFS between the 5-FU and Cisplatin and Carboplatin and Paclitaxel group whereas median DFS was comparable between the 5-FU and Cis-

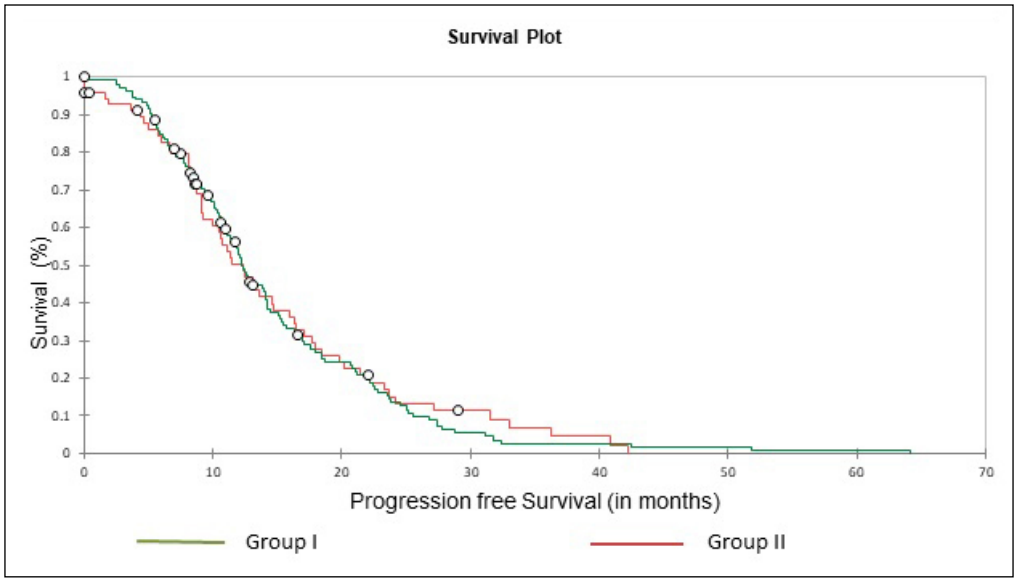

Fig. 3. The Kaplan-Meier progression-free survival estimates for Group I (Carboplatin & Paclitaxel) and Group II (5FU & Cisplatin) treated patients with esophageal cancer (p=0.909).

platin group (11.1 months) and the Carboplatin and Paclitaxel group (9.7 months). The results of this study suggest that the Carboplatin-based regimen is the preferred regimen for patients with potentially curable EC. Toxicity, excluding haematological events, occurred less frequently and was in generally mild in nature in the Carboplatin and Paclitaxel group compared to the toxicity rates observed in patients treated with 5-FU and Cisplatin regimen.

CONCLUSIONS

This is one of the few studies comparing the two chemotherapeutic regimens (Carboplatin and Paclitaxel *vs.* 5-FU and Cisplatin) for the treatment of EC in our state. Not much data is available with respect to comparison of two drug regimens used for EC, so this study gives an insight into the survival and adverse-effect profile of the two regimens especially in the Kashmiri population. The current study suggests that OS and PFS is not significantly different among the two treatment regimens in EC patients and Carboplatin and Paclitaxel regimen is relatively safer in comparison to 5-FU and Cisplatin regimen in terms of toxicities. However, the use of Carboplatin and Paclitaxel is associated with significantly more hematologic grade III toxicities compared to 5-FU and Cisplatin. Although the present study is not a randomized trial, the results support the claim that the Carboplatin-based regimen is superior to the Cisplatin-based regimen regarding toxicity of treatment and treatment compliance and a preferred treatment for patients with other comorbidities.

The study has certain limitations including a smaller number of patients, selection biases and the retrospective design. The other important limitation is that the patients were not randomized, which could have led to differences in patient characteristics between the treatment groups.

Financial Support:
There was no financial support for this study.

Ethics Approval:
The Ethical Approval was obtained from IEC SKIMS, vide No: SIMS 1131/IEC- SKIMS/2017-159.

Consent to Participate:
As the dataset was obtained by reviewing medical records of the patient, participant consent was not required as per the guidelines of IEC, SKIMS, although it was confirmed that all patients had signed written informed consent before undergoing treatment.

Consent for Publication:
The consent for publication has been provided by all the authors.

Availability of Data and Material:
The datasets generated during and/or analysed during the current study are not publicly available due to confidentiality reasons. This study included patients diagnosed with EC and making their identity public is a breach of trust and unethical. However, the data can be availed from the corresponding author on reasonable request.

Conflict of Interests:
The authors declare no conflicts of interest.

Author Contributions:
The study plan was charted out by NT in coordination with MML. NN collected and analyzed the data under the direct supervision of MML and NT. The first draft of this manuscript was prepared by NN and revised by NT. MML reviewed the final draft of this manuscript.

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