MAR Oncology and Hematology (2025) 5:01

Research Article

Comparison of the Toxicity Profile and Clinical Efficacy of two Concurrent Chemoradiotherapy Regimes in treatment of Elderly Patients with Esophageal Carcinoma: A Prospective Study.

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Received: 24 December 2024

Published: 22 January 2025

Abstract

Background: *Esophageal cancer, a leading cause of global cancer-related deaths, requires standard chemotherapy treatment. While studies show comparable efficacy in older adults, they face increased chemotherapy toxicity risks. The issue is similar with radiotherapy. However, clinical trials predominantly involve younger individuals, leaving an optimal treatment regimen for older esophageal cancer patients undefined.*

Methods: *The study included 97 esophageal cancer patients aged ≥65. All received 50.4 GY external beam radiation over 5 weeks. Of these, 53 patients had 5-Fluorouracil/Cisplatin (first and last week of radiation), while 54 had Paclitaxel/Carboplatin AUC 2 (weekly) with radiation. A standardized follow-up schedule included assessments at 3, 6, 12-, 24-, 36-, and 60-months post-treatment.*

Results: *A total 97 patients were enrolled in this study between July 2015 to May 2020. In both the groups, majority of the subjects were between 65 to 69 years. The rate of febrile neutropenia was higher in 5FU/Cisplatin arm (80% vs 56.8%). Cardiovascular toxicities were less commonly seen in both groups with no significant difference in grade of toxicity. Among gastrointestinal toxicities, nausea/ vomiting was common in both groups but grade 2 or higher was common in 5fu/ Cisplatin arm. Diarrhea was also commonly noted in 5FU/Cisplatin arm. Most common neurological toxicity was peripheral sensory neuropathy that was common in paclitaxel/carboplatin arm. There was no significant difference between the two groups with regards to overall survival and disease-free survival at 3 year and at 5 year of follow up*

Conclusions: *Concurrent chemoradiotherapy with 5FU/Cisplatin is equally effective to paclitaxel/carboplatin in terms of treatment response, OS, or DFS in elderly patients with oesophageal squamous cell cancer.*

Keywords: *Oesophageal cancer, concurrent chemoradiotherapy, 5-Fluorouracil/Cisplatin, Paclitaxel/Carboplatin, efficacy, toxicity.*

Introduction

Esophageal cancer (EC) is the sixth most common cause of cancer-related deaths and the eighth most common cancer worldwide. Current estimates suggest that approximately 500,000 new esophageal cancer cases are diagnosed, and more than 400,000 related deaths occur annually worldwide. This rising incidence worldwide has been reported [1] with a considerable change in the morphologic appearance of the tumors. To date, squamous cell carcinomas still account for most esophageal cancers, however in recent years the incidence of adenocarcinomas has increased notably [2] EC develops mainly in individuals aged >50 years, and the number of older patients with EC in India is increasing concomitantly with the aging of the population. [3-6]. Chemotherapy remains a standard component of cancer treatment. The literature is replete with studies that demonstrate that older adults experience similar chemotherapy efficacy. However, these patients are also at increased risk for chemotherapy toxicity compared with younger adults. [6-8] Furthermore, older adults are less likely to be offered chemotherapy because of concerns about their capacity to endure treatment. [9-10] Radiotherapy (RT) is of particular benefit to older and frail cancer patients as an alternative to surgery. It is widely used with curative and palliative intent. But older adults are less likely to be offered chemoradiation because of concern regarding their ability to tolerate the treatment [9,11] and due to the associated comorbidities [12]. Despite the increasing number of older patients with EC, the majority of clinical trials have involved only, or mostly, younger patients [13]. Although some studies have focused on older patients [14], these involved a relatively limited number of subjects and a single arm [15,16]. In addition, older patients have high rates of morbidity and mortality [17-18]. The optimal regimen of chemotherapy concurrent with radiation has not yet been established. Standard combinations consist of platinum salts (cisplatin [CDDP]) with fluoropyrimidines (e.g., 5-FU) combined with RT for both preoperative or definitive cure. More recently, treatment regimens including taxanes have been developed but none of them have been compared with conventional treatment, in older patients. Therefore, an optimal treatment regime for older patients with EC has yet to be established.

Multifactorial predictive models have focused primarily on hematologic end points, such as neutropenia [19,20] , febrile neutropenia [21,22] , and anemia [23]. The need for prospective models of chemotherapy tolerance that incorporate clinical measures such as comorbidities, cognition, depression, and nutrition has been emphasized [24]. Thus, we performed this study using two combinations of chemoradiotherapy (CTRT) regimens for operable or unresectable EC. The primary aim of this study was to compare the toxicity profile of two CCRT regimes, identify the risk factors for development of such toxicities and to compare the clinical outcome in elderly patients.

Methods

The study was conducted in the Department of Radiotherapy, Sher-i-Kashmir Institute of Medical Sciences (SKIMS), Srinagar, India. A total number of 97 patients with esophageal cancer and having age ≥ 65 years that reported to Regional Cancer Centre, Sher-i-Kashmir Institute of Medical Sciences were enrolled in the study. All patients received external bean radiation of total dose of 50.4 GY in 26 fractions over a period of 5 weeks. Among 97 patients, 53 patients received injection 5-Fluorouracil (750-1000mg/m^2)/ Cisplatin (75-100mg/m^2) with radiation (during first and last week of radiation) and 54 patients received inj. Paclitaxel (50mg/m^2) / Carboplatin AUC 2 (weekly) with radiation.

Ethical permission

The study was approved by the ethical committee of Sheri Kashmir Institute of medical sciences.

Inclusion criteria

1. Patients aged ≥ 60 years
2. Histopathologicaly documented squamous cell esophageal cancer
3. Stage of disease I to III,
4. Planned to be treated with concurrent chemoradiation,
5. Eastern Cooperative Oncology Group (ECOG) Performance status ≤2.

Exclusion criteria

1. Patient having previously received any chemotherapy/ radiotherapy or
2. ECOG Performance status ≥3
3. metastatic (stage IV) Disease, or
4. having such co morbidity that are contraindicated for chemotherapy or radiation were

After enrolling patients in the study complete pretreatment assessment was done which included:- Complete history taking and physical examination, Presence of co morbidity, Drug history, Baseline investigation(chemistry profile and complete blood count, CBC and imaging), Histopathological conformation, Height / weight / BSA of patient, WHO ECOG performance status.

Systems that were Assessed for Toxicities as per CTCAE [25]

1.Heamatological system 2. Cardiovascular system 3.Gastrointestinal system 4.Hepatobiliary system

5.Nervous system 6.Renal system 7.Skin 8.Vascular system 9.Metabolism and nutrition disorder.

A standardised, minimal follow-up schedule was defined, with clinical assessments at 3, 6, 12, 24, 36, and 60 months after treatment. Upper GI endoscopy was mandatory at 6 month after treatment. The study protocol mandated CT of the thorax and liver ultrasound or CT of the abdomen at 12 and 36 months as a minimum.

Statistical Analysis

The data was analyzed statistically with the help of statistical software SPSS v20 and Minitab. All the continuous variables of the study were represented by descriptive statistics and all the categorical variables in terms of frequency and percentage. Also, the categorical variables analyzed with the help of chi square test and continuous variables analyzed with the help of independent t-test. Data was presented by means of bars and pie diagram. All the results will be discussed at 5% level of significance.

Results

A total 97 patients were enrolled in this study between July 2015 to May 2020. Patient characteristics are summarized in Table 1. In 5FU/Cisplatin arm, 44 patients (83%) were in age group 65-69year, 9 patients (16.98%) were in 70-75year. In paclitaxel/carboplatin group, 39 patients (72%) patients were on 65-69 year age group, 10 patients (18.5%) were in 70-75 year age group, 5 patients (9.3%) were > 75year. In 5fu/cisplatin group, 33patients were male and and 20 patients were female where as in pacli/carb group, 35 patients were male and 19 were females.22 patients (42%) had ECOG 0 PS and 31 patients (58%) has PS 1-2 in 5FU/cisplatin group where as in pacli/carb group, 24 patients had (45%) had PS 0 and 30 patients (55%) had PS 1-2. stage ii was common in both arms (38 (72%) vs 32 (59.2%)). Tumor length was more the 5cm in both groups. Most of the patients did not underwent resection in both groups and documented reason was 1: proximal location of tumour (50%), 2. medically inoperable due to co-morbidities or 3. Patients refused to under surgery. All the patients completed prescribed dose of radiation (50.4 Gy) in both arms. Baseline laboratory parameters of all enrolled patients are summarized in Table 2. All patients received total radiation dose of 50.4GY by conventional technique (2D-RT).

Toxicity assessment:- In both groups, toxicity was assessed from first week of treatment. Commonly seen toxicities are summarized in table 3. Anemia was noted in both groups but grade of toxicity was higher in 5FU/cisplatin arm (grade 3/4 58% vs 24%), rate of febrile neutropenia was higher in 5FU/Cisplatin arm 80%

vs 56.8% with significant p value 0.456. Cardiovascular toxicities were less commonly seen in both groups with no significant difference in grade of toxicity. Among gastrointestinal toxicities, nausea/ vomiting was common in both groups but grade 2 or higher was common in 5fu/ Cisplatin arm (grade 2 in 47% and grade 3/4 in 25%) where as grade 1 was common in Paclitaxel/carboplatin arm (52%). Diarrhea was also commonly noted in 5FU/Cisplatin arm 23 (43%) and only 12(22%) had diarrhea in paclitaxel/carboplatin arm (p value=0.445). Mucositis was seen in 28 patient (52%) in 5FU/Cisplatin group and grade 3/4 was seen in more patients (10(19%)) as compared to 5 patients (10%) in paclitaxel/carboplatin group which was statistically significant (p value 0.468). dry mouth was another GI toxicity that was commonly seen in paclitaxel/carboplatin group then 5fu/cisplatin arm (67% vs 31%) with p value 0.024. Most common neurological toxicity was peripheral sensory neuropathy that was common in paclitaxel/carboplatin arm (37 patients (68%) vs 8 patients (15%)) with statistically significant difference (p value <0.001). in vascular system, flushing was seen in 18 patients (35%) in 5FU/Cisplatin arm where is none of the patient in paclitaxel/carboplatin arm showed any grade of flushing. (p value= 0.028). Skin hyperpigmentation was the most common dermatological toxicity seen 33 patients (62%) in 5FU/cisplatin arm and grade 2 was common where as in paclitaxel/carboplatin group, only 4 patients (7.4%) had skin pigmentation (p value <0.001). more than one toxicity was seen in many patients.

Temporal variations of statistically significant toxicities are noted in Table 4. In 5fu/cisplatin arm, hematological toxicities were commonly seen in second and fifth week, where as in paclitaxel/carboplatin are, these toxicities were commonly noted in 3rd and 4th week. CNS toxicities were also noted in 3rd and 4th week in paclitaxel/carboplatin arm. Skin hyperpigmentation was seen at the end of first and fifth week in 5fu/cisplatin arm. Treatment interruptions were also noted (table 5) . interruption in treatment was common in paclitaxel/ carboplatin arm then 5FU/CISPLATIN group (40% vs 25%) and interuption were more than 1-week inj paclitaxel arm. It was explained as most patients in taxane arm develop toxicity during 3rd week so in weekly chemotherapy arm patient needed rest to overcome the toxicity that's why interruption was needed and that too was >1week. In 5fu/cisplain arm 2 patients died due to treatment related events. 1 developed severe bone marrow depletion and sepsis and other died due to neutropenic colitis.

Treatment Outcome

In patients who were not operated, all patients were offered a structured follow-up at our institution including at least clinical examination, endoscopy and CT chest every three months for the first two years and in 6–12-month intervals thereafter. At 3-month, upper GI Endoscopy was done in both groups. Patients having no

residual disease on EGD were greater in 5FU/CISPLATIN arm then taxane arm but difference was not statistically significant (TABLE 6). Disease progression was seen in 2 (6%) and 4(11%) patients in 5FU/Cisplatin and paclitaxel/carboplatin arm respectively. 4 patients among them were treated with chemotherapy as per the institutional protocol and 2 patients refused further treatment. Imaging (CECT chest/abdomen/pelvis) was done in all patients, in 5fu/cisplatin arm, 20 patients (63%) were disease free, 8 patient (25%) had loco regional disease and 2 patients(6%) shows metastasis, where as in taxane arm, 21 patients (58) were disease free, 10 patients(28) had loco regional disease and 5 patients(14%) developed metastasis. The difference was statistically nonsignificant. DFS was assessed at 3 year and difference was statistical insignificant (60%vs 50%; p value 0.43). There was no significant difference in Overall survival at 3 year (41% VS 39%; p value 0.442) and at 5 year (25% VS 23%; p value 0.291) in 5FU/CISPLATIN and paclitaxel/carboplatin arm respectively.

Table 1. Baseline patients' characteristics

	Arm1 5FU/CISPLATIN N =53		**ARM 2** PACLI/CARB N=54		P VALUE
	N	%	N	%	
Age (years)					
65-69	44	83	39	72	
70-75	9	16.9	10	18.5	0.175
> 75	0	0	5	9.3	
ECOG performance score					
0	22	42	24	45	0.93
1-2	31	58	30	55	
Gender					
MALE	33	62.2	35	64.9	0.869
FEMALE	20	37.7	19	35.2	
Stage					0.878
I	6	11.3	9	16.7	
II	38	71.6	32	59.2	
III	9	16.9	13	24.1	
Tumor grade					
Well differentiated	7	13.2	8	14.8	0.087
Moderately differentiated	24	45.2	28	51.8	
Poorly differentiated	18	33.3	12	22.2	
Unavailable	4	7.5	6	11.1	

Length of tumour					
<5cm	12	23	18	34	0.32
>5cm	41	77	36	66	
Surgical resection					
Yes	21	40	18	34	0.52
No	32	60	36	66	
Pathological response					
Complete	8	36	7	39	0.08
Partial	7	32	8	45	
No response	6	27	3	17	

TABLE 2. Laboratory parameters

Parameter		**Mean**	**SD**	**Min**	**Max**
CBC	Hemoglobin (g/dl)	12.4	1.73	8.9	16
	TLC (cells×10^9/L)	6.8	1.73	3.4	12.5
	ANC (cells×10^3/µL)	4.2	1.26	1.8	8.9
	PLT(cell×10^3/µL)	190.4	75.01	1.03	456
KFT	UREA(mg/dl)	25.7	7.33	10	47
	CREAT(mg/dl)	0.85	0.20	0.4	1.52
LFT	BIL(mg/dl)	0.77	0.76	0.1	8
	ALT (U/L)	23.8	7.22	8	42
	ALP (IU/L)	103.7	33.74	59	355
	T.PROTIEN (g/L)	7.0	0.75	5	8.9
	ALB(g/L)	4.1	0.73	2.8	6.4

Table 3. Comparison of toxicities between two arms

SYSTEMS ASSESED	Group 1 (RT+5fu/cisplatin) n=53					Group2 (RT+paclitaxel/carboplatin) n=54					P value
	Grade of toxicity N(%)					Grade of toxicity N(%)					
	1	2	3	4	5	1	2	3	4	5	
Hematological											
Anemia	10(19)	10(19)	23(43.3)	8(15)	0	24(45)	7(13)	10(19)	3(5.5)	0	**0.004**
Febrile neutropenia	2(4)	30(57)	8(15)	2(4)	0	9(16)	16(30)	5(9)	1(1.8)	0	0.456
Cardiovascular											
Palpitation	3(6)	4(8)	0	0	0	2(4)	3(5.5)	0	0	0	0.992
Sinus bradycardia	0	2(4)	0	0	0	1(2)	0	0	0	0	1.000
Gastrointestinal											
Nausea/vomiting	16(30)	25(47)	7(13)	2(4)	0	28(52)	11(20)	5(9)	0	0	0.733
Diarrhea	10(19)	7(13)	6(11)	0	0	7(13)	5(9)	0	0	0	**<0.001**
Mucositis	5(9)	13(25)	7(13)	3(6)	0	2(4)	12(22)	4(8)	1(2)	0	0.468
Dry mouth	3(6)	13(25)	0	0	0	10(18)	25(45)	2(4)	0	0	**0.024**
Neurological											
Peripheral sensory neuopathy	2(4)	6(11)	0	0	0	4(7)	22(41)	9(16)	2(4)	0	**<0.001**
Vascular											
Flushing	2(4)	16(31)	0	0	0	0	0	0	0	0	**0.028**
hypotension	3(6)	10(18)	1(1.8)	0	0	4(8)	5(9)	3(5)	0	0	0.958
Skin											
Alopecia	2(4)	13(25)	0	0	0	4(7)	10(19)	0	0	0	0.616
Skin hyperpigmentation	2(4)	30(56)	1(2)	0	0	1(2)	3(5.4)	0	0	0	**<0.001**
General				‘							
Fever	6(11)	0	0	0	0	4(8)	3(5.5)	0	0	0	**0.307**
fatigue	9(17)	0	0	0	0	2(4)	4(8)	1(2)	0	0	0.989

Table 4. Distribution of carcinoma Esophagus cases according to the temporal variation of statistically significant Chemo (radio) therapy Induced Toxicities in 2-arms (till treatment completion)

Temporal parameters	GROUP/ARMS																Statistical remark
	5FU/Cisplatin N=53								Paclitaxal/Carboplatin N=54								p-value
	Hematological Toxicity		CNS toxicity		Derma toxicity		Vascular toxicity		Hematological toxicity		CNS toxicity		Derma toxicity		Vascular Toxicity		
	N.	%	N.	%	N.	%	N.	%	N.	%	N.	%	N.	%	N.	%	
I[ST] WEEK	3	6	3	6	13	25	6	11	2	3.7	2	3.7	0	0	0	0	0.0016
2[ND]WEEK	10	19	0	0	0	0	0	0	3	5.4	4	7.4	3	6	0	0	0.098
3[RD] WEEK	7	13	0	0	0	0	0	0	16	29.7	19	35.1	0	0	0	0	0.005
4[TH] WEEK	3	6	0	0	0	0	0	0	10	18.9	7	13	0	0	0	0	0.447
5[TH] WEEK	20	38	3	6	20	37.7	10	18.7	3	5.	3	5.2	0	0	0	0	0.001
TOTAL	43	80	6	12	33	62.5	16	30.1	34	63	35	64.8	3	6	0	0	

Table 5. Distribution of carcinoma Esophagus cases (2arms) according to treatment interruption and mortality during treatment

		Group/Arms				Statistical Remark
		5FU/Cisplatin N=53		Paclitaxel/Carbolpatin N=54		
		N	%	N	%	p-value
Treatment Interruption	Yes	13	25.0	22	40	0.343
	No	40	75.0	32	60	
Duration of interruption	≤ 1 Week	13	100.0	7	31.3	0.013
	> 1 Week	0	0.0	15	68.1	
Mortality during treatment		2	3.7%	0	0	0.448s

Table 6: Comparison of treatment outcome between two arms

Response evaluation after completion of CCRT	Groups/arms				Statistical remark
	5FU/CISPLATIN +RT N=32		PACLITAXEL/CARB +RT N=36		P value
	N	%	N	%	
EGD AT 3 month No residual disease Residual disease progression	 24 6 2	 75 19 6	 23 9 4	 64 25 11	0.064
Imaging No disease Locoregional diasease Metastasis	 20 8 2	 63 25 6	 21 10 5	 58 28 14	0.321
DFS at 3 year YES NO	 19 13	 60 40	 18 18	 50 50	0.43
OS at 3 year	13	41	14	39	0.442
OS at 5 year	8	25	7	23	0.291

Table 7. Previous Studies of Radiotherapy with a Fluorouracil-Based Regimen and a Taxane-Based Regimen for Elderly Patients with esophageal squamous cell cancer.

Study	type	patholo gy	N	AGE	Stage	treatment	ORR %	Median OS (Months)	OS % at 2 yr	Results
Hu 2016 (43)	retrospecti ve	Scc	202	18-75	IIb-IIIC	CCRT with PF(97) CCRT with PP(105)	30.9 52.4	23.1 33.9	47.6 61.9	PP>PF
Zhang 2016(40)	retrospecti ve	SCC	317	-	II-IVa	CCRT with PF(156) CCRT with DP(161)	- -	21 29	38 57	DP>PF
Zhao 2012(39)	retrospecti ve	SCC	90	18-70	II-Iva	CCRT with PF(45) CCRT with DP(34)	53.3 73.3	22.3 43.2	42 59	DP>PF
Zhu 2017(42)	prospectiv e	SCC	86	18-70	II-IVa	CCRT with PF(41) CCRT with	87.3 84.4	- -	86.2 69.1	DP=PF

						DP(45)				
Honing 2014(41)	prospective	SCC/AC	102			CCRT with PF(47) CCRT with PC(55)	- -	16.1 13.8	27 35	PC=PF
Sun 2016(44)	retrospective	SCC	179	42-76	II-IVb	CCRT with PF(96) CCRT with TB(83)	63.5 71.6	23 21	43 40	PC=PF
Fang 2017(45)	retrospective	SCC	86		II-IVa	CCRT with SC(41) CCRT with PP(41	82.9 82.9	20 21	40 43	SC=PP
Huang 2020(46)	retrospective	SCC	42	65-76	I-IVB	CCRT with PF(24) CCRT with DP(22)	66.7 81.8	27.8 34.4	52 72	DP=PF
current	prospective	SCC	97	65 above	I-III	CCRT with PF(53) CCRT with PC(54)	75 64	43 39	41 39 at 3 year	PF=PC

Abbreviations: n = number; AC = adenocarcinoma; CCRT= concurrent chemoradiotherapy; DP = docetaxel and cisplatin; PF = 5-fluorouracil and cisplatin; PC = paclitaxel and carboplatin; PP = paclitaxel and cisplatinum; SC = S-1 plus cisplatin); FB = fluorouracil-based regimen; TB = taxane-based regimen

Discussion

Surgery is considered as a first choice of treatment for most squamous cell carcinomas of the esophagus. However, major surgery is not appropriate for every elderly patient and definitive radiotherapy offers an effective alternative for these patients. Based on the results of recent clinical studies, the role of Chemo-radiotherapy (CRT) is evolving in settings where surgery is not feasible (25). Many physicians are tempted to alter the treatment strategy in populations with a supposed lower life expectancy in order to prevent acute toxicities that may deteriorate the patient's general condition. It has been shown that thoracic radiation therapy can be well-tolerated by those aged 70 and older (26). In the present study, 97 patients with esophageal cancer were enrolled and they were subdivided in three age groups (Table-1). Of the 97 patients, 53 patients received 5FU/Cisplatin with radiation and 54 patients received Paclitaxel/Carboplatin with radiation over a period of 5 weeks. In both groups, Hematological and non-hematological toxicities were noted as per Common

terminology criteria for adverse events (CTCAE) (25), and treatment outcome in terms of DFS and OS was also assessed at 3year and 5year. Patients in both groups received radiation in two phase (2D-RT) ; phase I 40GY in 20 fractions and In Phase II 10.4GY in 6 fractions). Common hematological toxicities i.e. anemia and febrile neutropenia were studied in detail (Table-2). Anemia was found in both groups, but in 5FU/Cisplatin group, grade 3 anemia was common (43.8%) which was comparable to study conducted by SE Anderson et al where grade 3 anemia was common (38%) (49). In Paclitaxel / Carboplatin group, grade 1 anemia was common (45%). The difference was statistically significant **(p value = 0.004).** Febrile neutropenia developed in 42 patients (76%) in 5FU/Cisplatin with radiation group and grade 2 was commonly seen (57%), which is comparable to the study conducted by FARID FATA et al where grade 2 neutropenia was common and was seen in 63% patients. (27) Whereas in Paclitaxel/Carboplatin with radiation group, 35 patients (73%) developed febrile neutropenia and here also grade 2 was common (30%). There was no statistically significant difference between development of neutropenia in two treatment arms. Palpitations developed in both arms equally 5 patient (9.5%) in Paclitaxel group and 7 (14%) patients in 5FU/ cisplatin arm. Sinus bradycardia was seen in 2 patient (4%) in 5FU/Cisplatin group which is comparable to the results of study conducted by Talaptra el al where sinus bradycardia developed in 6 % patients who received infusion 5FU. (28)

Gastrointestinal toxicities are commonly seen with cytotoxic chemotherapy which gets enhanced with concurrent use of radiation. In the present study, we assessed common gastrointestinal toxicities like nausea/ vomiting, diarrhea, mucositis and dry mouth. (Table-2). In 5FU/Cisplatin group, 50 patients (92%) developed nausea/vomiting and among them grade 2 was commonly seen in 25 patients (47%), Our results were contrarily to the results of the study conducted by Takashi Uno, KolchiIsobe et al where nausea/vomiting was seen in only 32 .72% and all had grade 1 toxicity.(29) Where as in Paclitaxel/Carboplatin group,44 patients (81%) developed nausea/vomiting, among them grade 1 was common (52%), the intergroup difference in development of these toxicities was statistically insignificant. In 5FU/Cisplatin group, 23 patients (43%) developed diarrhea, Whereas in Paclitaxel/Carboplatin group, 12 patients (22%) developed diarrhea. Our results were similar to the study conducted by T. Ruhstaller L. Widmer et al were diarrhea developed in 20% of patients receiving Paclitaxel/Carboplatin with radiation. (30) Difference between two groups was statistically significant**.**

Mucositis is a major non-hematological complication seen in patients receiving radiation to esophagus and it gets worsened with addition of cytotoxic chemotherapy. It is associated with significant morbidity, pain, odynodysphagia, dyseugia and subsequent dehydration and malnutrition.(31) In the present study mucositis was observed in 28 patients (53%) in 5FU/Cisplatin group, among them grade 2 was common (25%), it was

similar to the results of study conducted by Ken Kato, Kei Muro et al were mucositis developed in 49.4% of patients receiving 5FU/Cisplatin with radiation.(32) Where as in Paclitaxel/Carboplatin group, 19 patients (36%) developed mucositis, among them 12 patients (22%) had grade 2, 4 patients (8.7%) had grade 3 and 1 patient (2.7%) had grade 1 toxicity. It was similar to the study conducted by Nadia Haj Mohammad et al where in total 25% developed mucositis and grade 2 was common. (58) Physiological decline in renal function may also contribute to development of mucositis in these elderly patients. (33))

Feeling of dry mouth was noted in 16 patients (31.25%) receiving 5FU/Cisplatin with radiation and among them 13 patients (25%) had grade 2. Whereas, in Paclitaxel /Carboplatin with radiation group, 32 patients (68.5%) had feeling of dry mouth, out of them 25 patients (45%) had grade 2. It was observed that grade 2 toxicity was more common and was more so in Paclitaxel/Carboplatin with statistically significant difference (p value 0.024).

General disorder like fever and fatigue are known toxicities in patients receiving chemo-radiation and in our study 6 patients (11%) developed grade 1 fever in 5FU/Cisplatin group and none had higher grade. It was contrary to the results of study conducted by Bryan H. Burmeister et al where only 3% patients developed fever and all had grade 3 toxicity. (34) Fatigue was observed in 9 patients (17%) receiving 5FU/Cisplatin with radiation and all had grade 1 toxicity. Whereas in Paclitaxel/Carboplatin group, 7 patients (14%) developed fatigue, among them grade 2 was common in 8% patients. It was similar to the results of study conducted by Nadia Haj Mohammad et al where fatigue was found in 9% of patients receiving concurrent chemo radiation with Paclitaxel/Carboplatin. (33).

Peripheral neuropathy resulting from both axonal degeneration and demyelination is a DLT (dose limited toxicity) that is dose-dependent and cumulative. (35) In this study we assessed peripheral sensory neuropathy which was observed in 8 patients (15%) in 5FU/Cisplatin group and 11%had grade 2 toxicity. Whereas in Paclitaxel /Carboplatin group, 37 patients (68.5%) had peripheral sensory neuropathy, and among them 41% had grade 2 and 16% had grade 3 toxicity. Results were comparable to the study conducted by Jaffer A Ajani et al where neuropathy was observed in 51.42% patients. (36) Chemotherapy induced peripheral neuropathy (CIPN) was more common in Paclitaxel/Carboplatin group, and

difference between two groups was statistically significant (p value <0.001).

Skin toxicities like alopecia and hyper pigmentation are common toxicities of most chemotherapy agents. In this study, alopecia was observed in both groups (29% in 5FU/Cisplatin and 26% in Paclitaxel/Carboplatin group) and was statistically insignificant. Whereas skin hyper pigmentation developed in 33 patients (62.5%) in 5FU/Cisplatin group and grade 2 was seen in 56% cases. it was similar to the results of the study conducted

by Arunima Gupta, Avijit Hazra, et al where about 58.8% patients developed skin hyperpigmentation. (37) Whereas in Paclitaxel /Carboplatin group, only 4 patients (7.4%) had skin hyper pigmentation. Skin hyper pigmentation was common in 5FU/Cisplatin group and difference between two groups was statistically significant. (p value <0.001)

In 5FU/Cisplatin group, Chemo radiation induced hematological toxicities were commonly noticed in 5th week (38%) followed by 2nd (19%) and 3rd week (13%%). Whereas in Paclitaxel/Carboplatin group, these were commonly noticed at 3rd week (29.7%), followed by at 4th week (18.9%). Similarly, peripheral sensory neuropathy was common in 3rd week of treatment (35.1%) followed by 4th week (13%) in Paclitaxel/Carboplatin group. Whereas in 5FU/Cisplatin arm, it was common during First and 5th week of treatment (6%) each. Dermatological toxicity (skin hyper pigmentation) was common in 5FU/Cisplatin arm and most commonly developed at 5th week of treatment (37.7%) followed by first week (25%) whereas in Paclitaxel/Carboplatin group, 3 patients (6%) developed skin hyper pigmentation at 2nd week of treatment. Vascular toxicity like flushing was commonly noticed at 5th week of treatment (18.7%) followed by in First week (11%) in 5FU/Cisplatin arm.

Temporal difference in appearance / development of treatment related toxicities between two groups was statistically significant in first, 3rd and 5th week with significant p values**.** Treatment interruption was seen in 13 patients (25%) and none had >1 week of interruption among them in 5FU/Cisplatin group. Whereas in Paclitaxel /Carboplatin group, 22 patients (40%) had interruption in treatment and among them 15 patients (68.1%) had interruption > 1 week of duration.

Response evaluation was done with upper GI endoscopy after 3 month of completion of CCRT, and 75% of patients in 5fu/cisplatin arm had complete response which is similar to the study conducted by Sadamoto Zenda et al where 68% patients showed complete response on EGD after treating with 5FU/cisplatin concurrent with RT(38) Previous studies on the outcomes of radiotherapy combined with 5-Fu/ platinum and taxane/platinum in SCC patients are listed in Table 7 (39-46). Median survival time for 5Fu arm is 43 months versus 39 months in paclitaxel arm, which is contradictory with the results of three previous retrospective studies. In a randomized trial reported in 2012 by zhu et al (39), CCRT with a docetaxel/cisplatin regimen led to a higher response rate and better survival than CCRT with a 5-Fu/cisplatin regimen in patients with esophageal carcinoma (median OS: 43.2 months versus 22.3 months). A previous retrospective study [26] also showed that patients treated with the cisplatin/paclitaxel regimen displayed a definitive advantage over those treated with the cisplatin/5-Fu regimen (median OS: 33.9 months versus 23.1 months; median PFS: 15.9

months versus 13 months). In our study, DFS at 3 year was slightly higher in 5FU arm (60% vs 50%) but difference was statically insignificant. OS at 3 year and 5 year was comparable between 5FU/cisplatin arm and paclitaxel/carboplatin arm (41%vs39% and 25% vs 23% respectively). In above mentioned studies, OS was seen at 2 year where as our study is having longer follow up and Overall survival was estimated at both 3 and 5 year. . Although the patients in our study were older than those described in previous studies, the clinical efficacy after treatment with CCRT was similar to that observed in younger cohorts. This finding was also reported in a previous study (17). Therefore, elderly patients should not be excluded from intensive treatments based on age alone.

Conclusion

In conclusion, the results from the current trial indicate that CCRT with a 5FU/Cisplatin is equally effective to paclitaxel/carboplatin in terms of treatment response, OS, or DFS in elderly patients with oesophageal squamous cell cancer.

Acknowledgements: None

Funding/support: None

Author's contribution: SS and MAK conceptualized the study, performed the data collection, analysed the data and prepared the manuscript; AW and PG helped in providing technical inputs to the analysis and assisted in drafting the manuscript. All the authors were involved in all aspects of the conduct of the study and manuscript preparation.

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