ORIGINAL ARTICLE

EFFICACY AND TOXICITY OF CARBOPLATIN/PACLITAXEL BASED CHEMORADIATION FOR LOCALIZED OESOPHAGEAL CANCER

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Background: The management of Oesophageal and Gastroesophageal junction cancers is challenging. Multimodality therapy with carboplatin/paclitaxel based chemoradiation (CRT) and surgery shows improved efficacy. In this study, we wanted to establish the efficacy and safety of CRT for neoadjuvant and radical treatment of localized oesophageal cancer. **Methods:** Patients with oesophageal cancer, registered between September 2013 and October 2014 were reviewed retrospectively. Toxicity and efficacy analysis in the form of radiological response rate, R0 resection rate, Progression free survival (PFS) and overall survival (OS) was performed on 102 patients who received radical carbo/pacli induction chemotherapy followed by CRT. Impact of Surgery was seen on PFS and OS. **Results:** Males and females were 71 (51.1%) and 68 (48.9%) respectively, with squamous cell carcinoma being the predominant histology (92%). Majority of patient belonged to T3/4 and N1 stage. Grade III/IV thrombocytopenia, neutropenia, anaemia, febrile neutropenia requiring hospitalisation, non-hematologic toxicities were noted in 13 (12.8%), 18 (17.7%), 18 (17.7%), 1 (1%), 1 (1%), patients respectively. Complete Radiological response, partial response, Stable disease, progressive disease was seen in 6 (5.9%), 51 (50%), 23 (22.5%) 8 (8.7%), respectively. Resection was done in 29 (28.4%). Complete and partial pathological response were seen 19 (65.5%), 10 (34.4%), respectively. PFS at 40 and 80 weeks was 90%, 73%, respectively and OS at 80 weeks was 86%. PFS at 40 and 80 weeks was 100% and 90.5%, respectively with resection, while it was 86% and 65%, without resection (P value 0.015). OS at 40 and 80 weeks was 100% (both) with resection, while it was 96% and 79.5% weeks without resection. (*p*-value 0.034). **Conclusions:** Carbo/pacli based CRT is effective with acceptable toxicity profile in treating localised oesophageal cancer as both as Radical CRT and as a part of multimodality therapy. For definitive results, long term follow up and prospective analysis are required.

Keywords: Oesophageal neoplasms; Chemoradiotherapy; Survival; Toxicity

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INTRODUCTION

Oesophageal cancer and cancer of the gastro-oesophageal junction remain a challenging disease to treat. Despite advances in management, long term outcomes remain poor with an estimated 2-year survival for localized disease of 40–50%.[1] This declines sharply with increase in the size of tumour, nodal involvement and poorly differentiated histology.[2] Multimodality treatment with chemo-radiation in addition to surgery has led to significant improvement in outcomes of localized esophageal cancer over the last two decades.[3] Pre-operative chemotherapy and pre-operative chemo-radiation are now considered standard for this disease. Chemo-radiation (CRT) has also been used in un-resect able, non-metastatic oesophageal cancer with impressive outcomes which in some cases, parallel the surgical series.[4] The mainstay of chemo-radiation for oesophageal cancer has been the Cisplatin/5-fluorouracil combination.[5,6] These two drugs are highly active and have a synergistic effect when combined with radiation due to their radio-sensitization properties.

Cisplatin/5-FU based treatment is effective but has significant toxicities.[7] For Cisplatin; these include significant risk of vomiting, risk of nephrotoxicity, neuropathy and ototoxicity, as well as the need to give rapid IV fluids to maintain a high urine output which may be problematic in the elderly or in patients with compromised cardiac function.

5-FU is fairly well tolerated with low risk of vomiting or myelosuppression but it can occasionally cause coronary vasospasm leading to coronary ischemia, and cardiac arrhythmias.[8,9] Administration of 5-FU requires prolonged infusion over several days, requiring either hospital admission or indwelling central venous catheters. These can lead to complications including dislocation, thrombosis, and infection. Capecitabine, an oral pro-drug of 5-FU may avoid some of these issues, but compliance with oral medications is difficult in patients with oesophageal cancer undergoing chemo-radiation due to poor swallowing as a result of the disease as well as the treatment effects.

A number of other chemotherapeutic agents have been shown to be highly active in oesophageal cancer. Taxane based combinations have shown excellent response rates and long term outcomes in gastric and oesophageal cancers.[10,11] Carboplatin/paclitaxel combination has been shown to

be effective in oesophageal cancer, not only as a systemic treatment option but also as a potent radio-sensitizer.[12,13]

The aim of the study was to assess the efficacy and the toxicity of Carboplatin/paclitaxel (CP) combination for neoadjuvant and radical treatment of localized non-metastatic oesophageal cancer in combination with radiation and surgery.

MATERIAL AND METHODS

Analysis of case records for patients registered with a histo-pathological diagnosis of oesophageal cancer at Shaukat Khanum Memorial Cancer Hospital & Research Centre, Lahore from September 2013 to October 2014, was carried out. A total of 139 patients received Carboplatin/paclitaxel (CP) based regimen with or without radical radiation. Out of these 102 patients with non-metastatic disease treated with radical intent were included for final analysis. This study was approved by hospital ethical committee. Data were collected from hospital information system.

The primary objectives of the study were response rate, R0 resection rate, progression free survival. The Secondary objectives were overall survival, acute and long term treatment toxicity in patient with pathologically proven diagnosis of adeno-carcinoma or squamous cell carcinoma of the oesophagus.

Overall survival (OS) was measured from the date of diagnosis to last follow up or death from any cause.[14] Progression-free survival (PFS) was determined as an interval between the date of diagnosis to clinical or radiological progression or death, whichever occurred first.[14]

Eligibility criteria for the study was histologically proven squamous cell carcinoma or adenocarcinoma of the oesophagus or gastro-oesophageal junction not extending beyond gastric cardia and fundus with disease stage I to III (cT2—cT4, cN0—cN3. M0).

Biopsy specimens were available in all cases and were reviewed by two pathologists, who confirmed that all cases were histologically proven squamous cell carcinoma or adenocarcinoma of the oesophagus or gastro-oesophageal junction.

The patients had upper GI endoscopy and CT chest/abdomen with contrast done as staging workup, prior to starting treatment. PET-CT and endoscopic ultrasound (EUS) were done as staging workup where indicated.

Patients were treated with induction chemotherapy consisting of 2 or more, 3 weekly cycles of Carboplatin/Paclitaxel - Carboplatin (AUC 5) and Paclitaxel (200 mg/m2) followed by concurrent chemo-radiation, which consisted of weekly Carboplatin/Paclitaxel (Carboplatin AUC 2, Paclitaxel 50 mg/m2). Patients received radical radiotherapy at doses ranging between 45–50 Gy in 25 fractions.

All patients underwent planning CT and 3D conformal treatment planning. GTV was based on extent of tumour including involved lymph nodes seen on available investigations (CT, PET-CT, endoscopy and EUS). CTV consisted of involved lymph nodes as in GTV along with a 3 cm margin superior and inferior to the primary tumour along the oesophagus/gastro-oesophageal junction and 0.5cm margin in the axial plan around oesophagus to include subclinical para-oesophageal lymph nodes. PTV consisted of 1.5cm margin all around CTV. Radiation therapy was delivered with megavoltage equipment with photon energies of equal to or greater than 6 MV. A multi-leaf collimator or individually shaped blocks were used to shape the irradiation portal according to the planning target volume. The prescription dose was specified at the ICRU 50/62 reference point, which was the isocentre for most patients. The daily prescription dose was 1.8–2 Gy at the ICRU reference point and the 95% isodose encompassed more than 95% of PTV. Tissue density inhomogeneity correction was used. Response evaluation imaging with contrast enhanced CT scan was done 6–8 weeks from the end of concurrent chemo-radiotherapy. Records were noted for date of first clinical visit, age at diagnosis, gender, the extent of disease on first presentation by history and physical examination, TNM stage, chemotherapy type, number of cycles and duration of chemotherapy, dose, and fractions and duration of radiotherapy. Toxicity profile was assessed according to CTC version 4 criteria.

Toxicity assessment was done at each chemotherapy visit during induction chemotherapy, on weekly basis during chemo radiation and at 6 weeks' post completion of CRT. Side effects were graded according to CTC version 4.

Records were noted for radiological response at the end of CRT, resection whether done or not, EOT resection intervals, resection margins, pathological response.

The patients were followed for evidence of disease progression in the form of radiological or biopsy proven progression and were stratified into local, loco regional and distant progression. Patient status –alive or dead, at last clinic visit was noted.

SPSS-10 was used for data analysis. Survival curves were constructed by using Kaplan Meier method.

RESULTS

Of the total 139 patients identified there were 71 (51.1%) males and 68 (48.9%) females. The predominant histologic type was Squamous cell carcinoma. Majority of patient belonged to T3/4 and N1 stage. There were 18 (12.9%) patients in our study who had metastatic disease at presentation. Most of the

patients had disease involving the middle and lower oesophagus. See table-1 for details of patient baseline characteristics.

The subgroup of patient (n=102) who received treatment with induction chemotherapy followed by chemo radiation with 45 Gy and above (completed intended treatment) were noted to have Complete Radiological response in 6 (5.9%), partial response in 51 (50%), Stable disease in 23 (22.5%) and progressive disease in 8 (8.7%) patients.

Amongst the whole cohort who received treatment with intended radical approach with or without surgery, 80 (78.4%) patient did not suffer any recurrence. Local, loco regional and distant recurrences were seen in 9 (8.8%), 5 (4.9%) and 8(8.7%) patients, respectively. Seventy-four (72.5%) patients were alive, 12 (11.8%) died and there were 16 (15.7%) patients whose status was unknown on follow up. (Table-2)

The progression free survival (PFS) in this cohort at 40 and 80 weeks was 90% and 73%, respectively and the overall survival (OS) was 86 % at 80 weeks, respectively (Figure-1 & 3)

Only 29 (28.4%) out of 102 patients underwent resection amongst these patients. Amongst them complete pathological response was seen 19 (65.5%), partial pathological response in10 (34.4%). None of the patients was noted to have similar stage disease or Progressive disease. R1 resection was found in only 1 patient. (Table-3)

PFS and OS were analysed depending upon the resection status. It was noted that the PFS at 40 and 80 weeks was 100% and 90.5%, respectively with resection, while it was 86% and 65%, respectively without surgical resection. This difference was statistically significant with *p*-value of 0.015. (Figure-2). It is noted that median PFS was not reached in 100 weeks in resected patient while it was around 90 weeks for those patients who were treated without resection.

The OS at 40 and 80 weeks was 100% (both) with resection, while it was 96% and 79.5% weeks respectively without surgical resection. This difference was statistically significant with *p*-value of 0.034. (Figure-4). Median OS was not reached in patients with or without resection in 100 weeks of follow up. We noted that grade III/IV thrombocytopenia was observed in 13 (12.8%), grade III/VI neutropenia in 18 (17.7%), grade III/IV anaemia in 18 (17.7%), febrile neutropenia requiring admissions in 1 (1%). Amongst nonhematologic toxicities none if the patients were reported to develop grade III/IV mucositis whereas only 15 (14.7%) had grade I/II mucositis. Other non-hematologic grade III/IV toxicities including vomiting, diarrhoea, fatigue, body aches were noted in 1 (1%) patient's. (Table-4)

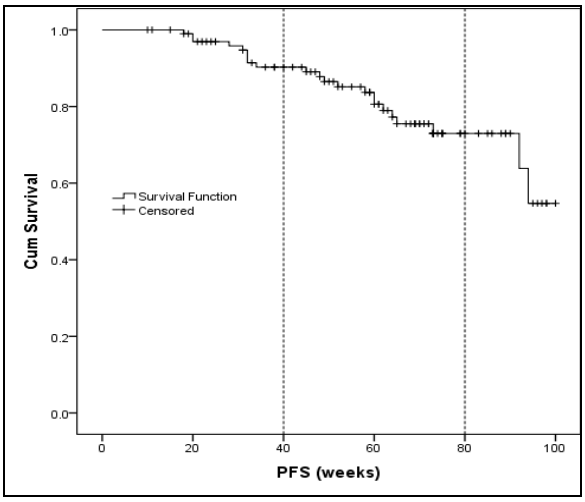

Figure-1: PFS for radical chemoradiation

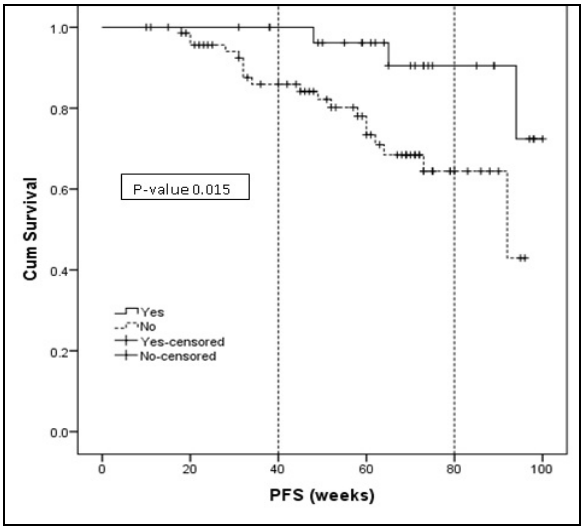

Figure-2: PFS for resection

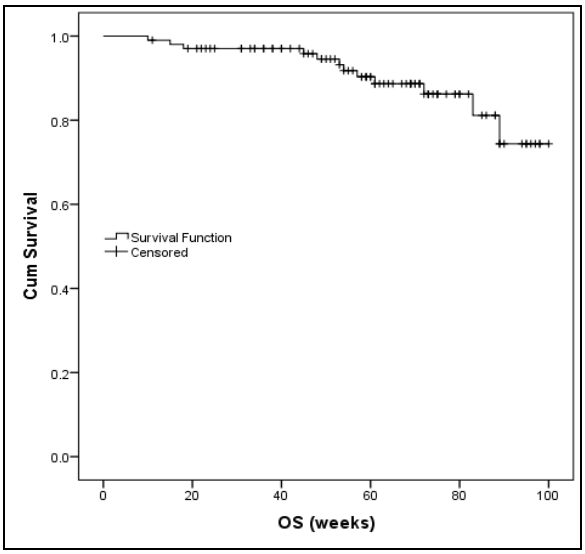

Figure-3: Overall survival for chemoradiation

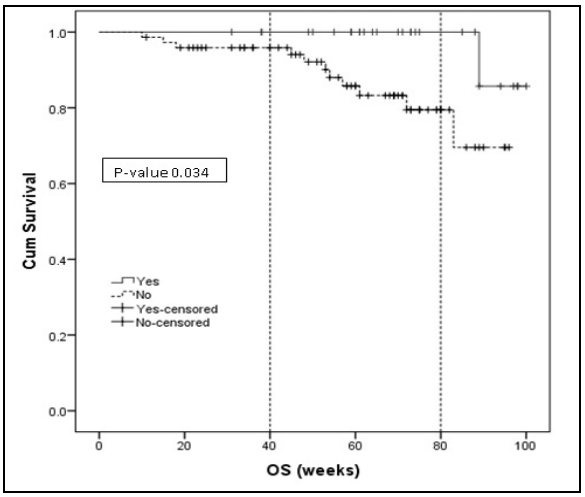

Figure-4: Overall survival for resection

Table-1: Baseline characteristics

Gender	Male n (%)	71 (51.1)
	Female n (%)	68 (48.9)
Histology	Squamous cell carcinoma n (%)	128 (92)
	Adenocarcinoma n (%)	10 (8)
T stage	T2 n (%)	2 (1.4)
	T3 n (%)	70 (50.4)
	T4 n (%)	67 (48.2)
N stage	N0 n (%)	32 (23)
	N+ n (%)	107 (76.9)
M stage	M0 n (%)	121 (87.1)
	M1 n (%)	18 (12.9)
Tumor location	Upper 1/3 n (%)	4 (2.9)
	Middle 1/3 n (%)	59 (42.4)
	Lower 1/3 n (%)	76 (54.7)
Resection	Done n (%)	33 (23.7)
	Not Done n (%)	106 (76.3)

Table-2: Treatment outcomes

Radiological Response	**n (%) 102 (100)**
CR	6 (5.9)
PR	51 (50)
SD	23 (22.5)
PD	8 (7.8)
Unknown	12 (13.6)
Resection done	
Yes	29 (28.4)
No	73 (71.6)
Patient Status	
Alive	74 (72.5)
Dead	12 (11.8)
Unknown	16 (15.7)
Site of Recurrence	
None	80 (78.4)
Local	9 (8.8)
Loco regional	5 (4.9)
Distant metastasis	8 (7.8)

Table-3: Pathological response rate

Pathological Response status	n (%) 29 (100)
Complete Response	19 (65.5)
Partial Response	10 (34.4)
No response	0 (0)
R 0 margin	28 (96.55)
R 1 margin	1 (3.5)

Table-4: Toxicities

Side Effect	**Grade**	**n (%)102 (100)**
Thrombocytopenia	None	39 (38.2)
	1	32 (31.4)
	2	18 (17.6)
	3	12 (11.8)
	4	1 (1)
Neutropenia	None	54 (52.9)
	1	24 (23.5)
	2	6 (5.9)
	3	12 (11.8)
	4	6 (5.9)
Anaemia	None	25 (24.5)
	1	28 (27.5)
	2	31 (30.4)
	3	17 (16.7)
	4	1 (1)
Febrile Neutropenia Requiring Hospitalisation	Yes	1 (1)
	No	101 (99)
Mucositis	None	87 (85.3)
	1	10 (9.8)
	2	5 (4.9)
Other Toxicity	None	52 (51)
	1–2	49 (48)
	3–4	1 (1)

DISCUSSION

Oesophageal and GOJ tumours are usually treated with multimodality therapy with neoadjuvant chemo-radiation or chemotherapy followed by surgery in standard clinical practice. The major evidence favouring the efficacy and safety of concurrent chemo radiation with carbo/pacli came from CROSS trial.[3] The experimental arm in CROSS trial consisted of concurrent chemoradiation with low dose weekly chemotherapy. The total radiation dose in the CROSS trial was limited to 41. 4Gy. In contrast in this single centre study we gave 2–3 cycles of induction chemotherapy with full systemic doses of carbo /pacli followed by CRT with 45–50 Gy. This study of neoadjuvant induction chemotherapy with carbo/pacli followed by concurrent chemo radiotherapy showed good radiological response rates, PFS, OS amongst patients with localized oesophageal and gastro oesophageal junction cancer. This study has shown that 78.4% patients had no disease progression on serial scans after neoadjuvant chemo-radiotherapy.

RO Resection and Pathological CR rate in CROSS trial in chemo radiotherapy arm was 29% and 92% respectively.[3] However in this study the RO resection and pathological CR was 96.55% and 65.5% for patients who underwent resection. But the number of patient who underwent resection in this study were not comparable to those in the Cross trial. The reasons for not undergoing resection were co morbid conditions, patient preferences and limitations of surgical resources.

There were very few patients who underwent surgery, but those who did, had very good loco regional control rates. In this study the major modality of treatment, that is, surgery was not carried out in a large number of patients but even then, the overall PFS & OS

was reasonable amongst all the patients who were treated with CRT only and the results have shown that they improved further in those who completed multimodality therapy. RTOG 85-01[4] and INT 0123[1] were the landmark trials which established the efficacy of definitive CRT with Cisplatin and 5-Flourouracil. The 5-year Overall survival was 26% in the RTOG 85-01 trial with chemo radiation, while in INT 0123the median survival was in the range of 13–18%, however, in this study the median PFS and OS were not reached in up to median 100 weeks of follow up. However, on subset analysis it was noted that those patients who did not undergo surgery after radical treatment median PFS was approximately 90 weeks. This CRT regimen was fairly well tolerated as there was 12–18% frequency of grade III & IV hematologic toxicity and very few hospitalizations. Non-hematologic toxicities were rarely noted. However, being a single centre study with a short duration of follow up are the main limitations of the study. We conclude that CP based systemic induction chemotherapy followed by chemoradiation is effective and well tolerated regimen for oesophageal cancer. In particular, patients who are not candidates for surgical resection, this regimen is a potential alternative to the traditional Cisplatin/5-FU based chemoradiation and needs to be tested with current standard in a prospective randomised trial.

CONCLUSIONS

Systemic induction chemotherapy with Carboplatin/paclitaxel followed by Carbo/pacli based CRT is effective in treating localised oesophageal cancer both as definitive CRT and as a part of multimodality therapy. It is fairly well tolerated with hematologic toxicities requiring transfusional support being the main toxic effects. Prospective randomised trials comparing with traditional Cisplatin/5-FU based treatment are required.

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AUTHORS' CONTRIBUTION

MQ: Questionnaire preparation, Data collection, Data analysis, Script writing. YI: Questionnaire preparation, Data collection. KM: Data collection. FB: Statistical analysis. AK: Conception of basic study theme, Questionnaire preparation, Mentorship.

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