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Docetaxel, Cisplatin, Leucovorin and 5- Fluorouracil versus Leucovorin, 5-Fluorouracil, and Cisplatin as Neoadjuvant Chemotherapy Followed by Chemoradiation in Head and Neck Cancer

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Abstract **Original Research Article**

Background: HNSCC is the fifth most common cancer in the world and one of the most prevalent cancers in Bangladesh. Despite significant improvement in radiotherapy, the high incidence of loco-regional recurrences is a major challenge for radiation oncologists. This study was done to compare the response and toxicity of Docetaxel, Cisplatin, Leucovorin and 5- Fluorouracil (TPLF) vs Leucovorin, 5- Fluorouracil, and Cisplatin (LFP) as neoadjuvant chemotherapy followed by concurrent chemo-radiation with Cisplatin in the treatment of locally advanced head and neck cancer of squamous cell carcinoma. ***Materials and Methods***: This study was carried out among 60 patients of locally advanced of head and neck cancer at Khwaja Yunus Ali Medical College & Hospital, Sirajganj from January 2015 to December 2015. In Arm-A, 30 patients received three cycles of neoadjuvant chemotherapy with Docetaxel 75 mg/m^2 on D1, Cisplatin 75 mg/m^2 on D1, Leukovorine 30 mg on D1-D3, 5-Flourouracil 750 mg/m^2 on D1-D5 and in Arm B 30 patients received neoadjuvant chemotherapy with Cisplatin 75 mg/m 2 on D1, Leucovorine 30 mg on D1-D3, 5-Flourouracil 750mg/m 2 on D1-D5 3 cycles with three weeks interval followed by concurrent chemoradiotherapy with 66 Gy in 33 fractions and weekly Cisplatin 40 mg/m 2 started on the first day of radiation. ***Results:*** Most of the patients were male and middle-aged group. In Arm-A, 21 patients (70%) showed complete response whereas in Arm-B regimen complete response was noticed in 16 patients (53.3%) which was statistically significant; however, partial responses were significantly more found in Arm-B. Regarding toxicity, with Arm-A patients experienced slightly more toxicities in comparison to Arm-B which was statistically non-significant. ***Conclusion:*** So, it could be concluded from this study that the therapeutic gain was better obtained in Arm-A compared to Arm-B in patients with locally advanced head and neck cancer.

Keywords: HNSCC, cancer, radiotherapy, Cisplatin, Leucovorine.

INTRODUCTION

Globally, head and neck cancer is the seventh most frequently occurring cancer, which accounts for more than 660,000 new cases and 325,000 deaths per year. It occurs in both developed and developing regions but more commonly seen in developing countries. Around 90% of head and neck cancers are squamous cell carcinoma in type and they arise from the epithelial lining of the oral cavity, larynx and pharynx [1]. It was seen that, most common risk factors for head and neck cancer include tobacco in either smoke or smokeless form. Both tobacco and alcohol consumption have synergistic effect for carcinogenesis. Petroleum exposure is associated with pharyngeal cancer [2]. It was seen that, HPV most commonly associated with oropharyngeal carcinoma, especially tonsil in which HPV DNA was identified upto 60% [3].

In addition, smoking during radiotherapy resulted in reduced response rates and also caused mucositis and subsequently raised the frequency of treatment breaks for smokers [4]. Age and tumor staging were the factors of most prognostic importance; poor response rate after the age of 70 years increased local failure rate with increased tumor size [5].

A study described the evolution of treatment approach in management of head and neck cancer, which focused on surgical and nonsurgical organ preservation approaches which lead to recent options for chemoradiotherapy combination for locally advanced, inoperable head and neck cancers and surgery at residual or recurrence [6]. Recent trials have consistently demonstrated the superiority of combined treatment programs alone for local tumor control, organ preservation and enhancement of quality of life for the cancer patients [7]. In the Meta-Analysis of Chemotherapy in Head and Neck Cancer (MACHNC), the addition of induction chemotherapy using cisplatin plus fluorouracil (PF) to local treatment did not decrease locoregional failures, and it was associated with a small improvement in overall survival and distant failures. PF induction chemotherapy is not considered as a standard treatment in locoregionally advanced HNSCC, except in the case of larynx preservation, for which both PF induction chemotherapy and concomitant CRT are considered standard [8]. Nevertheless, investigators are continuously evaluating new regimens in the induction setting to improve ORR, PFS and OS. Among agents introduced in the 1990s, taxanes have shown great promise for the treatment of HNSCC. Phase III data are emerging to support combinations of docetaxel or paclitaxel with a platinum plus 5-fluorouracil as a new, more effective and less toxic standard combination for neoadjuvant chemotherapy. The clinical efficacy of neoadjuvant chemotherapy using a PF regimen doubled while a three-drug combination of taxane (docetaxel or paclitaxel), cisplatin, and fluorouracil (Tax-PF) is still undergoing evaluation in several randomized controlled trials (RCTs) with varying results [9].

The taxanes, docetaxel and paclitaxel act by promoting tubulin polymerization and the formation of stable microtubules affecting the normal mitotic process and leading to cell death. The clinical activity and safety of single-agent docetaxel have been established in several phase II studies in patients with advanced or recurrent head and neck cancer. Overall response rates were in the range of 21%–42%, and grade 3–4 neutropenia predictably was the most common toxicity. In patients with locally advanced head and neck cancer, the addition of docetaxel to PF-based induction therapy has resulted in consistently high overall response rates, in the range of 71%–100%, and very encouraging long-term survival rates [10].

Addition of Leucovorin to 5- FU can enhance the binding of 5-FU to an enzyme inside the cancer cells. As a result, 5-FU may stay longer and exert its anticancer effect on the cells. The antitumor effectiveness and tolerable toxicities of PFL regimen was demonstrated in head and neck cancer. Existing pharmacokinetic and cytokinetic studies have suggested that continuous infusion chemotherapy given concomitantly with radiation acts synergistically, resulting in a significant increase in tumor cell killing. In conclusion, LFP outpatient chemotherapy is a new and highly active regimen for advanced stage NPC patients. It is safe with tolerable toxicities [11].

In a first phase I/II study, The TPLF-5 regimen, in which docetaxel was combined with continuous cisplatin, 5-FU, and leucovorin during 5 days repeated every 4 weeks for three cycles, had a very high response rate (overall response rate 100%) but was abandoned due to excessive toxicity. The TPLF-4 regimen in which 5-FU and leucovorin were given during 4 days showed an overall response rate of 93% (CRR 63%). The toxicity was less than with the TPLF-5 regimen but 14% of cycles were associated with hospitalization for toxicity [12].

Another Japanese study looked at the combination of docetaxel, cisplatin, 5-FU, and l-leucovorin in 34 patients. In case of complete response after induction chemotherapy patients were treated with radiotherapy. The main hematologic toxicity was neutropenia (grade 3 or 4 in 18.7% of cycles). The most common non-hematologic toxicities included anorexia, stomatitis and alopecia. The clinical overall response rate was 88.2% (CRR 58.8%). After definitive locoregional therapy, 25 of 34 patients were disease free with preserved anatomy. Overall and progression-free survival rates at the 2-year follow-up were 92.8% and 75.3% respectively [13].

So far, our knowledge goes; no substantial works have been carried out previously in Bangladesh. The study may give us information about the proper management of advanced head and neck cancers. As a result, patients will be benefited from this study due to effective treatment.

MATERIALS AND METHODS

This quasi-experimental study was carried out during January 2015 to December 2015. It was conducted in KYAMCH Cancer Center, Khwaja Yunus Ali Medical College & Hospital, Enayetpur, Sirajgonj, Bangladesh. The study participants were patients with locally advanced squamous cell carcinoma of the head and neck treated with neoadjuvant chemotherapy TPLF or LFP followed by chemoradiation during this period. There were 2 arms in this study and each of the arms consisted of 30 patients. Purposive sampling technique was done, the patients who were histologically proven cases of locally advanced head and neck carcinoma

were finally enrolled in the study. Prior to commencement of the study, the research protocol was approved by the ethical committee of KYAMCH. The objectives of the study along with its procedure, alternative methods, risks and benefits of this study were explained to the patients in easily understandable local language and then informed written consent from the patients was obtained. It was assured that all information and records would be kept confidential and the procedure would be helpful for both patients and physicians in making decision for management. After cleaning and editing, all the relevant data were compiled on a master chart. Statistical analysis of the results was obtained by SPSS for Windows (IBM SPSS Statistics for Windows, version 22.0). Continuous data were expressed as mean ± SD and were compared by Student "t" test. Categorical data were expressed as number and percentage and were compared via the Chi-square test and Fisher's Exact tests. Two tailed $p<0.05$ was considered as significant.

SELECTION CRITERIA

A. Inclusion criteria:

- Patients of locally advanced head and neck cancer with stage III or IV disease without distant metastasis.
- Patients with histopathologically proven squamous cell carcinoma.
- Patients are required to have international union against cancer (UICC) performance status ECOG up to grade 2
- Age: 18 to 70 years.
- Hemoglobin should be more than 10 gm/dL or > 60%.
- Total WBC count more than or equal to 4000 cells/cmm
- Platelet count more than or equal to 100000cells/cmm.
- S. Billirubin level should be equal to or less than 1.5mg/dL
- ALT < 2.5 x ULN [10-40 U/L normal]
- S. Creatinine less than 1.5mg/dL
- Blood urea level less than 50 mg/dL

B. Exclusion criteria:

- Patients with history of prior chemotherapy or radiotherapy to the head and neck region.
- Initial surgery (excluding diagnostic biopsy) of the primary site.
- Patients with double primaries.
- Pregnant or lactating woman.
- Serious concomitant medical illness including severe heart disease, uncontrolled diabetes mellitus, hypertension or renal diseases
- Patients with uncontrolled infection.
- Prisoners.

C. Criteria for discontinuation of treatment:

- Patients' refusal to continue study participation.
- Occurrence of unacceptable toxicity necessitating major modification of treatment.

A structured data collection form was used as the research instrument. This was used for collection of information by interviewing and examining the patients. Besides these, hospital documents were also used. The main outcome variables were: tumor regression, short term clinical response rate and acute toxicities among the participants at the end of intervention.

Laboratory studies:

- Complete blood count
- Renal function test (serum creatinine, creatinine clearance rate).
- Liver function test (serum bilirubin, ALT, AST).
- ECG

Radiology and imagine studies:

- X-ray chest P/A view.
- Lateral view X-ray of the soft tissue of the neck
- CT scan / MRI of head and neck region
- USG of whole abdomen for metastatic workup

Others:

Fine needle aspiration cytology
Pan endoscopy
Biopsy

Treatment plan:

Neoadjuvant Chemotherapy

For Arm -A

1. Inj. Docetaxel 75 mg / m^2 IV on D1
2. Inj. Cisplatin 75 mg / m^2 IV on D1
3. Inj. Leucovorin 30 mg / m^2 on D1– D3
4. Inj. 5 –FU 750 mg / m^2 IV on D1–D5

3 weekly cycles for 3 cycles

For Arm-B

1. Inj. Cisplatin 75 mg / m^2 IV on D1
2. Inj. Leucovorin 30 mg / m^2 on D1 – D3
3. Inj.5 -FU 750 mg / m^2 IV on D1 – D5

3 weekly cycles for 3 cycles

Proper hydration was maintained and pre and post chemotherapy medication with antiemetic, steroid, ranitidine, will be given before and after chemotherapy. Followed by Chemoradiation for both arms which were started 3 weeks after completion of NACT with Inj. Cisplatin 40 mg/m^2/day IV 2 hours infusion on day 1, weekly schedule. It was started on the first day of radiotherapy, continued weekly. Any pre-existing dehydration was corrected prior to chemotherapy with hydration and dieresis. Antiemetics (Ondansetron and Steroid) were given prior to chemotherapy.

Radiotherapy:

Basic principle of radiotherapy is to cure the patient with minimal functional and structural impairment. Treatment planning involves accurate localization of the tumor and prescription of daily fractions of radiation for a specific period of time. For irradiation of head and neck, all the patients were treated by parallel opposed fields.

All patients were treated by radiotherapy in the following ways:

- Type of technique - SAD.
- Type of plan - 3D CRT.
- Site of radiation – Facio cervical.
- Machine - LINAC.
- Energy - Photon; 6 MV.
- Total dose – 66 Gy. in 33 fractions
- Dose /fraction – 200 cGy. on daily basis, 5 days per week
- Dose limit to spinal cord – 40 Gy

Follow up:

- Follow up 1 week after each cycle of chemotherapy.
- Weekly follow up during radiotherapy.
- Weekly during chemoradiation.

After completion of treatment – 1st follow up at 6th week, 2nd follow up at 12th week and 3rd follow up at 24th week.

Assessment of the treatment response:

Treatment response was assessed in the light of RECIST 1.1 (Response Evaluation Criteria in Solid Tumors) criteria, Toxicity was observed according to RTOG Cooperative group common toxicity criteria & common terminology criteria for adverse effects (CTCAE) version 4,0 (2010)

Medical and Supportive care during treatment:

Patients were managed individually as per their symptoms & requirement with antibiotics, analgesics, steroids, antihistamines, anti-emetics, vitamins, IV fluids and blood transfusion etc.

Patient assessment and evaluation after treatment:

Every patient was monitored weekly by CBC, platelet count and serum creatinine ALT, serum bilirubin during treatment and followed up to 6 months after completion of treatment. Size of the tumor was assessed by different imaging techniques. Oral mucositis, nausea, vomiting, hematological toxicities and renal toxicities were evaluated weekly during treatment according to "RTOG" toxicity criteria.

***RECIST:** Response Evaluation Criteria in Solid Tumors (RECIST) is a standard way to measure the response of a tumor to treatment.

Table 1: RECIST 1.1 Response [14]

Complete Response [CR]	Disappearance of all lesions and pathologic lymph nodes
Partial Response [PR]	• ≥30% decrease Sum of the Longest Diameters of the target lesion [SLD] • No new lesions • No progression of non-target lesions
Stable Disease [SD]	No Partial Response [PR] – No Progressive Disease [PD]
Progressive Disease [PD]	≥20% increase SLD compared to smallest SLD in study or progression of non-target lesions or new lesions.

***RTOG:** Radiation Therapy Oncology Group (RTOG) is a scoring system for side effects of radiotherapy.

Table 2: RTOG Scoring Criteria [15]

RTOG Scoring Criteria	Skin Changes
0	No change over baseline
1	Follicular, faint or dull erythema, epilation, dry desquamation, decreased sweating
2	Tender or bright erythema, patchy moist desquamation, moderate oedema
3	Confluent, moist desquamation other than skin folds, pitting oedema
4	Ulceration haemorrage, necrosis

***CTCAE:** Common Terminology Criteria for Adverse Events is a general guideline based on adverse events with unique clinical events of severity.

Table 3: CTCAE grading system [16]

Grade I	Do not require treatment
Grade II	Often require symptomatic treatment but are not life-threatening
Grade III	Potentially life-threatening if untreated
Grade IV	Actually life-threatening
Grade V	Ultimately leads to patient death

RESULTS AND OBSERVATION

Table 4: Socio-demographic characteristics and personal history of the respondents (n=60)

Characteristics	Arm-A (n/%)	Arm-B (n/%)	Fisher's Exact Test	*p*-value
Age group (years)				
31-40	2 (6.7)	1 (3.3)	0.814	0.541
41-50	7 (23.3)	8 (26.7)		
51-60	15 (50.0)	17 (56.7)		
61-70	6 (20.0)	4 (13.3)		
Gender				
Male	24 (80.0)	23 (77.0)		
Female	6 (20.0)	7 (23.0)		
Occupation				
Farmer	11 (36.67)	10 (33.33)		
Service holder	7 (23.33)	8 (26.67)		
Businessman	6 (20.0)	7 (23.33)		
Others	6 (20.0)	5 (16.67)		
Smoking status				
Yes	25 (83.3)	24 (80.0)	0.475	0.457
No	5 (16.7)	6 (20.0)		

Table 4 above shows the socio-demographic characteristics and personal history of the respondents. It is clearly evident that, maximum number of patients belonged to 51-60 age group in both the arms, that is 15 (50.0%) and 17 (56.7%) in Arm-A and Arm-B respectively. There was no statistical significance found. As far as gender is concerned, majority of participants were males in both arms, which is 24 (80%) and 23 (77.0%) in Arm-A and Arm-B respectively. In terms of occupation, most of the patients were farmers by profession, which is 11 out of 30 in Arm-A and 10 out of 30 in Arm-B. With regards to smoking status of the patients, 25 out of 30 in Arm-A and 24 out of 30 in Arm-B were found to have history of smoking, which means maximum patients had this habit. There was no statistical significance seen among the two arms.

Table 5: Distribution of the respondents according to their complaints (n=60)

Site	Arm-A		Arm-B		Total (n=60)	
	n	%	n	%	n	%
Pain in affected site	20	66.7	22	73.3	42	70.0
Dysphagia/ odynophagia	18	60.0	21	70.0	39	65.0
Swelling of neck node	17	56.7	18	60.0	35	58.3
Ulceration	16	53.3	14	46.7	30	50.0
Weight loss	10	33.3	11	36.7	21	35.0
Altered phonation/ hoarseness of voice	9	30.0	11	36.7	20	33.3
Hemoptysis	4	13.3	6	20.0	10	16.7
Trismus	2	6.7	1	3.3	3	5.0
Altered hearing/ otalgia	1	3.3	0	0.0	1	1.7

Table 5 above shows distribution of the respondents according to their initial complaints. It can be seen that, maximum patients in both the arms, which is 20 (66.7%) in Arm-A and 22 (73.3%) meaning a total of 42 out of 60 patients complained of pain in affected site initially. Other prominent complains after pain were dysphagia/odynophagia, swelling of neck node and ulceration. The least common complaints were trismus and altered hearing/otalgia which were seen in a total of 3 and 1 patients respectively.

Figure 1 below shows distribution of the patients according to staging of the disease in the two arms. In Arm-A, equal numbers of patients were in stage III & stage IV A (12 patients each). Six patients in this arm were in stage IV B. These numbers in Arm B were 11, 14 and 5 respectively. However, no statistical significance was observed in this regard ($p>0.05$).

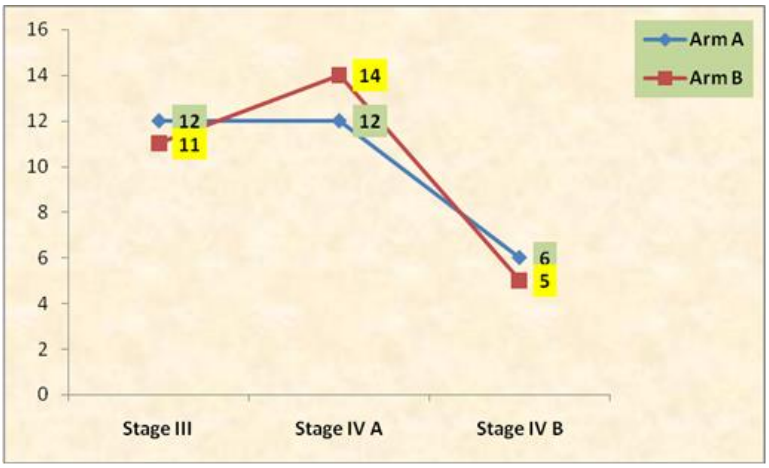

Figure 1: Distribution of the patients according to staging of the disease in both arms (n=60)

Table 6: Distribution of the respondents according to their responses after 3rd cycle Neo-adjuvant chemotherapy and follow-up (n=60)

Responses	Arm-A		Arm-B		*p*-value
	n	%	N	%	
After 3 cycles of Neo-adjuvant Chemotherapy					
Complete response	12	40.0	5	16.7	0.044
Partial response	18	60.0	20	83.3	
At 1st follow-up (after 6 weeks)					
Complete response	18	60.0	13	43.3	0.196
Partial response	12	40.0	17	56.7	
At 2nd follow-up (after 12 weeks)					
Complete response	20	66.7	15	50.0	0.190
Partial response	10	33.3	15	50.0	
At 3rd follow-up (after 24 weeks)					
Complete response	21	70.0	16	53.3	0.349
Partial response	4	13.3	8	26.7	
Stable disease	5	16.7	6	20.0	

Table 6 above shows distribution of the respondents according to their responses after 3 cycles of neo-adjuvant chemotherapy and follow-up. In Arm-A, twelve patients (40%) showed complete response (CR) whereas in Arm-B, complete response was noticed in five patients (16.7%); partial responses (PR) were 18 (60%) and 25 (83.3%) in the two arms respectively. Significantly more patients in Arm-A had shown CR than Arm-B patients ($p<0.05$) (Table 6). At 1st follow-up, 18 patients in Arm-A and 13 patients in Arm-B showed CR while at 2nd follow-up 20 patients in Arm-A and 15 patients in Arm-B showed CR. At 3rd follow-up, 21 patients in Arm-A and 16 patients in Arm-B showed CR. Stable disease was found in 5 and 6 patients in two arms respectively. These differences were not statistically significant.

Table 7: Distribution of the respondents according to their post-treatment response (n=60)

Status at last follow-up	Arm-A		Arm-B		*p*-value
	n	%	n	%	
Complete response	21	70.0	16	53.3	0.048*
Partial response	4	13.3	8	26.7	0.035*
Stable disease	5	16.7	6	20.0	0.251
Total	30	100.0	30	100.0	

*=statistically significant.

Table 7 above shows distribution of the respondents according to their post-treatment response. In Arm-A, twenty-one patients (70%) showed complete response (CR) whereas in Arm-B, complete response was noticed in sixteen patients (53.3%); partial responses (PR) were 4 (13.3%) and 8 (26.7%) in the two arms respectively. There were five (16.7%) stable disease in Arm-A and six (20%) stable disease in Arm-B. CR was significantly higher in Arm-A than Arm-B ($p<0.05$) while PR was significantly higher in Arm-B than Arm-A ($p<0.05$)

Table 8: Distribution of the respondents according to their toxicities during Neo-adjuvant Chemotherapy (n=60)

Toxicity	Grade	Arm-A		Arm-B		*p*- value
		n	%	n	%	
Oral Mucositis	Grade I	14	46.7	17	56.7	0.081
	Grade II	10	33.3	10	33.3	
	Grade III	6	20.0	3	10.0	
Neutropenia	No change	18	60.0	22	73.3	0.559
	Grade I	6	20.0	5	16.7	
	Grade II	6	20.0	3	10.0	
Nausea	Grade I	18	60.0	22	73.3	0.997
	Grade II	12	40.0	8	26.7	
Vomiting	Grade I	6	20.0	6	20.0	1.00
	Grade II	14	46.7	16	53.3	
	Grade III	10	33.3	8	26.7	
Diarrhoea	Grade I	22	73.3	24	80.0	0.611
	Grade II	6	20.0	6	20.0	
	Grade III	2	6.7	0	0.0	

Table 8 above shows distribution of the respondents according to their toxicities developed during neo-adjuvant chemotherapy. Regarding oral mucositis, there were fourteen grade 1 toxicities, ten grade 2 toxicities and six grade 3 toxicities in Arm-A, while in Arm-B there were seventeen grade 1, ten grade 2 toxicities & three grade 3 toxicities. Regarding neutropenia, there were six grade 1 and grade 2 toxicities in Arm-A while there were five grade 1 and three grade 2 toxicities in Arm-B. Most of the patients in both arms showed no changes regarding neutropenia toxicities. Nausea is compared during neo-adjuvant chemotherapy. There were eighteen grade 1 toxicities and twelve grade 2 toxicities in Arm-A, while in Arm-B there were twenty-two grade 1 toxicities and eight grade 2 toxicities. Regarding vomiting, toxicities there were six grade 1, fourteen grade 2 and ten grade 3 toxicities in Arm-A, while in Arm-B there were six grade 1, sixteen grade 2 and eight grade 3 toxicities. Diarrhoea is also compared during neo-adjuvant chemotherapy and there were twenty-two grade 1 toxicities and six grade 2 toxicities & two grade 3 toxicities in Arm-A, while in Arm-B there were twenty-four grade 1 toxicities and six grade 2 toxicities. These differences were statistically not significant (p>0.05).

Table 9: Distribution of the respondents according to their toxicities during radiotherapy (n=60)

Toxicity	Grade	Arm-A		Arm-B		*p*- value
		n	%	n	%	
Mucositis	Grade I	14	46.7	16	53.3	0.091
	Grade II	13	43.3	13	43.3	
	Grade III	3	10.0	1	3.3	
Skin reaction	Grade I	21	70.0	24	80.0	0.456
	Grade II	7	23.33	5	16.66	
	Grade III	2	6.67	1	3.34	
Nausea	Grade I	22	73.3	19	63.3	0.287
	Grade II	8	26.7	11	36.7	
Anaemia	Grade I	10	33.3	12	40	1.00
Dysphagia	Grade I	25	83.3	27	96.6	0.739
	Grade II	5	16.7	3	3.4	

Table 9 above shows distribution of the respondents according to their toxicities during radiotherapy. Toxicities were comparable between two arms but mucositis particularly grade III toxicity was more in Arm-A. Skin toxicities were more in Arm-B. There were 21 grade 1 toxicity, seven grade 2 toxicity and two grade 3 toxicity in Arm-A whereas these numbers were 24, 5 & 1 respectively. Grade 2 nausea was slightly higher in Arm-B than Arm-A. Like other toxicities, no significant differences were found regarding anaemia and dysphagia toxicities between the two arms.

DISCUSSION

In this study Arm A patients received three cycles of NACT with TPLF (Docetaxel 75 mg/m^2 on D1, Cisplatin 75 mg/m^2 on D1, Leukovorine 30 mg on D1-D3, 5-Flourouracil 750 mg/m^2 on D1-D5) and Arm B patient received NACT with PFL (Cisplatin 75 mg/m^2 on D1, Leucovorine 30 mg on D1-D3, 5-Flourouracil 750mg/m^2 on D1-D5) 3 cycles with three weeks interval followed by CTRT with 66 Gy in 33 daily fraction and weekly Cisplatin 40 mg/m^2 started on the first day of radiation.

The mean age of Arm-A patients was 56.73 (SD ± 8.05) years and that of Arm-B was 57.1 (SD ± 7.34) years. In Arm-A, out of thirty patients 24 (80%) were males and rest 6 (20%) were females. In Arm-B the number of males was one less than Arm-A. These findings are understandable because head & neck cancers mainly occur in middle age. Due to various factors including personal habits and genetic predisposition, males are particularly vulnerable to develop such cancers. Another study demonstrates similar findings with the current study [12].

After 3 cycles of Neo-adjuvant chemotherapy and before starting of radiotherapy in Arm-A 12 patients (40%) showed complete response (CR) whereas in Arm-B complete response was noticed in 5 patients (16.7%); partial responses (PR) were 25 (83.3%) and 18 (60%) in the two arms respectively. Significantly more patients in Arm-A had shown CR than Arm-B patients ($p<0.05$). In successive three follow ups, Arm-A patients showed more CR than Arm-B patients although the differences were not statistically significant.

In a study conducted in 2013, out of forty patients twenty-one patients received three cycles of NACT i.e. paclitaxel (175 mg/m^2) on Day 1, cisplatinum (30 mg/m^2) and 5-FU (600 mg/m^2) d2-d4 (TCF) and 19 patients received three cycles of NACT docetaxel (75 mg/m^2) on d1, cisplatinum (30 mg/m^2) and 5-FU (600 mg/m^2) d2-d4 at three week intervals, followed by concurrent weekly cisplatinum 30 mg/m^2 along with conventional external beam radiation of total tumor dose dose 66 Gy. Two weeks after completion of NACT complete response (CR) in TCF was 4.76%, partial response (PR) 80.9% and no response 9.5%. [17] Another study in 1994 illustrated that, PR after LFP chemotherapy were achieved in 5 of 27 (14%) and CR were in 27 (77%) of 35 [18].

Regarding post treatment responses, in Arm-A significantly more patients (21, 70%) showed complete response (CR) than Arm-B (16, 53.3%); whereas partial responses (PR) was significantly higher in Arm-B than arm-A ($p<0.05$). In a study done in 1999 reported response rates of 100% (61% CRs) with the TPFL-5 regimen and of 93% (63% CRs) with the TPFL-4 regimen. Recently, the same group also reported on an outpatient TPFL regimen, in which the 5-FU and leucovorin were again given over 4 days. The overall response rate with the regimen was 94%, with 44% CRs [12].

Another study shown, the clinical overall response rate to TPFL was 88.2%, with 58.8% CRs and 29.4% partial responses. After definitive locoregional therapy, 25 of 34 patients were disease-free with preserved primary tumor site anatomy. Overall and progression-free survival rates at the 2-year follow-up are 92.8 and 75.3% respectively [13].

Regarding follow-up, after 6 weeks, patients of both arms experienced constitutional symptoms almost identically except anorexia & dysphagia which were slightly higher in Arm-A.

Regarding toxicities, in this study oral mucositis is compared during NACT. There were 14 (46.7%) grade 1 toxicities, 10 (33.3%) grade 2 toxicities and 6 (20%) grade 3 toxicities in Arm-A, while in Arm-B there were 17 (56%) grade 1, 10 grade (33.3%) 2 toxicities & 3 (10%) grade 3 toxicities. This difference was statistically not significant ($p>0.05$). In a 2002 study, 70 patients were included and neoadjuvant chemotherapy given [19].

Neutropenia toxicity is compared during neoadjuvant chemotherapy in this study as well. There were 6 (20%) grade 1 and grade 2 toxicities in Arm-A while there were 5 (16.7%) grade 1 and 3 (10%) grade 2 toxicities in Arm-B. Most of the patients in both arms showed no changes regarding neutropenia toxicity. Statistically this difference was not significant ($p>0.05$). This finding is in agreement with the study findings by Diptirani Samanta *et al*., (2013) where they showed in DCF arm neutropenia grade II was 18.7% and also correlate with the study of Kose *et al*., (2011) [17, 20]. It is worth noting that Hitt *et al*., reported higher incidence of neutropenia in their study (grade 4, 14%; febrile neutropenia, 4%) [19].

Regarding nausea toxicities during neoadjuvant chemotherapy, there were 18 (60%) grade 1 toxicity and 12 (40%) grade 2 toxicity in Arm-A, while in Arm-B there were 22 (73.3%) grade 1 toxicity and 8 (26.7%) grade 2 toxicity. Statistically this difference was not significant ($p>0.05$). Jacinto et al. (2017) also found similar result [21].

Vomiting toxicities is compared in the present study. During neoadjuvant chemotherapy, there were 6 grade 1 toxicities, 14 grade 2 toxicities and 10 grade 3 toxicities in Arm-A, while in Arm-B there were 6 grade 1 toxicities, 16 grade 2 toxicities and 8 grade 3 toxicities. This difference was also statistically not significant ($p>0.05$).

In addition, during neoadjuvant chemotherapy, there were 22 grade 1 diarrhoea toxicities and 6 grade 2 toxicities & 2 grade 3 toxicities in Arm-A, while in Arm-B there were 24 grade 1 toxicities and 6 grade 2 toxicities. The patients with grade 2 diarrhoea toxicities had to manage by IV infusion of cholera saline and antibiotics. However, the differences were statistically not significant ($p>0.05$).

Different toxicities during radiotherapy were compared in the current study. Toxicities were

comparable between two arms but mucositis particularly grade III toxicity was more in Arm-A. Neutropenia was more in Arm-B. There were 21 grade 1 toxicities, 7 grade 2 toxicities and 2 grade 3 toxicities in Arm-A whereas these numbers were 24, 5 & 1 respectively. Grade 2 nausea was slightly higher in Arm-B than Arm-A. Like other toxicities no significant differences were found regarding anaemia and dysphagia toxicities between the two arms. These findings are in agreement with some other study findings [20].

CONCLUSION

In this study, addition of Docetaxel to Leukovorine, 5-Flourouracil & Cisplatin as neoadjuvant chemotherapy followed by concurrent chemoradiotherapy was found to be significantly more effective than Leucovorine, 5-Flourouracil & Cisplatin in locally advanced head and neck cancer. Regarding toxicity, Arm-A patients experienced slightly more toxicities in comparison to Arm-B. However, this difference was statistically non-significant. So, it could be said from this study that the therapeutic gain was better obtained in Arm-A as neoadjuvant chemotherapy compared to Arm-B in patients with locally advanced head and neck squamous cell carcinoma. The high response rates to Arm-A regimen justify further evaluation of these agents in the formal clinical trial.

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