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Response and Toxicity Outcomes of Induction Chemotherapy Followed by Concurrent Chemoradiotherapy Compared with Concurrent Chemoradiotherapy alone in Locally Advanced Oropharyngeal Squamous Cell Carcinoma

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Abstract
Treatment of oropharyngeal carcinomas significantly impact patient's quality of life for critical function in speech and swallowing. Though concurrent chemoradiotherapy (CCRT) is the established standard of care for inoperable disease, induction chemotherapy (IC) is still being investigated in attempt to decrease the chance of distant metastases and improve loco-regional control. This study was carried out among 82 patients of inoperable locally advanced OPSCC (stage III to IVB) from November, 2020 to October, 2021 who fulfilled the inclusion and exclusion criteria and distributed into two treatment arms by purposive sampling in BSMMU, NICRH and DHL. Arm A received IC with docetaxel / cisplatin / 5 fluorouracil (TPF) schedule followed by CCRT and Arm B received CCRT alone both with 3DCRT, 66Gy in 2Gy daily fraction, 5 fractions per week. Final responses were evaluated at 24 weeks after the treatment. In Arm A, 29 (70.7%) patients and in Arm B, 18 (43.9%) patients showed complete response (CR). Acute hematologic and non-hematologic toxic effects during chemoradiotherapy were almost similar in the two arms. In conclusion, Induction chemotherapy followed by concurrent chemoradiotherapy is more effective than concurrent chemoradiotherapy alone in terms of loco-regional control in inoperable locally advanced oropharyngeal squamous cell carcinoma with acceptable toxicities.
Keywords: *Induction chemotherapy, Concurrent chemoradiotherapy, oropharyngeal squamous cell carcinoma.*

Introduction

Oropharyngeal carcinoma comprises of carcinoma arising from any of the subsites - tonsils, tonsilar pillars, soft palate and base of the tongue. Squamous cell carcinoma is the most common histologic subtype comprising more than 95% of all oropharyngeal cancers.[1] Despite changes in epidemiology from smoking and alcohol history to human papilloma virus (HPV)-associated disease, oropharyngeal cancer remains one of the most common squamous cell carcinoma of the head and neck district.[2] The annual incidence of oropharyngeal cancer world-wide is morethan 98,412 cases with around 48,143 deaths each year. In Bangladesh, the estimated new cases of oropharyngeal cancer in 2020 are more than 3,852 (Globocan, 2020).[3] Concurrent chemoradiotherapy (CCRT) is the standard

treatment for individuals having inoperable locally advanced OPSCC.[4] Induction chemotherapy (ICT) is often used in clinical practice which is controversial despite the benefit observed in previous few studies.[5,6] The major criticism is whether IC could negatively impact on the subsequent optimal delivery of planned CCRT.[7] However, given the superiority of IC using taxane, several trials have directly compared TPF-IC followed by CRT with concomitant CCRT that favors use of IC.[8] Moreover, HPV etiology (HPV-positive) appears to be associated with better clinical outcomes, suggesting that intensification of treatment strategy may be necessary in patients with HPV-negative squamous cell carcinoma.[9,10] The addition of induction chemotherapy remains an appropriate approach for advanced disease with high risk for local or distant failure.[11] Induction chemotherapy has been advocated as distant metastasis is frequently a site of first failure for patients with loco-regionally advanced oropharyngeal cancer because loco-regional therapy (CCRT) has become so much moreeffective.[12,13]

Materials and Methods

From November, 2020 to October, 2021, a quasi-experimental study was performed among 82 patients with inoperable Stage III to IVB OPSCC in the Department of Clinical Oncology of Bangabandhu Sheikh Mujib Medical University (BSMMU), and the Department of Radiation Oncology, National Institute of Cancer Research and Hospital (NICRH), Dhaka and Oncology Unit Delta Hospital Limited, Mirpur, Dhaka. On November 11, 2020, the BSMMU Institutional Review Board (IRB) granted ethical approval (No. BSMMU/2020/9716). The study was carried out in line with the Helsinki Declaration. Criteria for inclusion: Patients with biopsy proven, inoperable locally advanced oropharyngeal squamous cell carcinoma; stage III-IVB (AJCC 8th Edition staging) Criteria for exclusion: Age below 18 years, Patients Eastern Co-operative Oncology Group (ECOG) performance status ≥ 2, History of prior chemotherapy or radiotherapy to the head and neck region, serious concomitant medical illness. Then patients were purposively divided between two arms (Arm A and Arm B). Before each patient's enrolment, a signed informed consent was obtained. To collect information, a data collection sheet was used. IC was given followed by CCRT in Arm A, while CCRT was given alone in Arm B. IC in arm A included Injection docetaxel 75 mg/m^2 IV on day 1, Injection cisplatin 75mg/m^{2}IV on day 1, Injection 5-FU 1000mg/m^2/day IV continuous infusion on day 1 to day 4, (3 weekly cycle for 3 cycles).[14] Adequate hydration and pre and post chemotherapy medications were maintained before and after chemotherapy. Both arms received CCRT with 66 Gray (33 fractions, 2 Gray/day, 5 days per week over 6.5 weeks).[15] Concurrent chemotherapy with injection cisplatin 40mg per m2 was administered weekly. Patients were monitored every three weeks during ICT and weekly during CCRT. The RTOG toxicity criteria were used to assess toxicity.[16] Patients were evaluated at week 6, 12 and 24 for the treatment responses by RECIST (Response Evaluation Criteria in Solid Tumors) criteria. Data was analyzed by the IBM SPSS software application for Windows. For comparing the response and toxicity outcomes, the Chi-square test was applied.

Results

The total number of participants in this study was 82, with 41 in each Arm A and B. The mean age of Arm A and Arm B patients was 57.12 (±4.43) years and 58.70 (±5.61) years respectively. The majority of patients in both arms have an ECOG score of one (73.16%). The primary site of majority of the patients was base of tongue 27 (65.85%) in Arm A and 24 (58.53%) in Arm B. Moderately differentiated was the most commonly observed histo-pathological differentiation in both Arm A 26 (63.4%) and Arm B 23 (56.09%). Total 53.65% of Arm A patients and 48.78% of Arm B patients were in stage IVA, whereas 36.60% of Arm A patients and 29.27% of Arm B patients were in stage IVB (see Table I). In Arm A, 29

(70.7%) patients showed complete response (CR) and in Arm B, CR was observed in 14 (43.9%) patients. Partial responses (PR) were 4 (9.7%) and 11 (26.8%) in two arms respectively. Stable diseases (SD) were 5 (12.2%) in Arm A and 4 (9.8%) in Arm B. There were 3 (7.4%) progressive disease (PD) in Arm A and 8 (19.5%) in Arm B. Treatment response was statistically significant between two groups ($p<0.05$) (see Table IV). According to the intention to treat analysis, lost to follow-up patients were considered as progressive disease. Oral mucositis was frequently observed during and after treatment in both arms. In Arm A, 10 (24.4%) and 25 (61.0%) patients developed grade 2 and grade 3 oral mucositis respectively vs 11 (26.8%) and 20 (48.8%) patients In Arm B respectively. Regarding xerostomia, only grade 1 and grade 2 toxicities were observed which was statistically insignificant ($p>0.05$). Grade 2 and grade 3 dysphagia was slightly higher (46.3% vs 63.3%) in Arm B. Total 23 (56.1%) patients in Arm A and 24 (58.5%) patients in Arm B, 09 (21.9%) patients in Arm A and 08 (19.5%) patients in Arm B showed grade 1 and grade 2 dysgeusia respectively. In Arm A, 19 (46.3%) and 06 (14.6%) patients developed grade 2 and grade 3 dermatitis respectively.

In Arm B, 15 (36.5) and 04 (09.7%) patients developed grade 2 and grade 3 dermatitis respectively. These differences in toxicities between the arms were not statistically significant ($p>0.05$). In terms of neutropenia, 3 (7.3%) patients in arm A and 1 (2.4%) patient in arm B had grade 3 neutropenia (see Table V). Majority of patients, 56 (68.29%) in both arms completed the therapy within expected schedule. Total 25 (60.97%) patients in Arm A and 31 (75.60%) patients in Arm B completed the radiotherapy within the expected time. However, 16 (39.02%) patients in Arm A and 10 (24.39%) patients in Arm B had delay of 1 week. Overall, the result was statistically insignificant (p value =0.154). Considering the chemotherapy, majority of the patients were able to tolerate the prescribed schedule of the chemotherapy, 36 (87.80%) patients in Arm A and 38 (92.68%) patients in Arm B (p value =0.659) (see Table III).

Table I: Characteristics of the patients.

Characteristics	Arm A (n=41)	Arm B (n=41)
Age (mean± SD)	57.12 (±4.43)	58.70 (±5.61)
Sex (%) Male Female	30(73.2%) 11(26.8%)	29(70.7%) 12(29.3%)
Clinical stage (%) Stage III Stage IVA Stage IVB	04 (9.75%) 22(53.65%) 15(36.60%)	09(21.95%) 20(48.78%) 12(29.27%)
Differentiation (%) Well Moderate Poor	13 (31.72%) 26(63.4%) 02(4.87%)	17(41.48%) 23(56.09%) 01 (2.43%)
Primary sites (%) Base of tongue Tonsils Soft Palate Pharyngeal wall	27(65.85%) 12(29.29%) 01(2.43%) 01(2.43%)	24(58.53%) 15(36.61%) 01(2.43%) 01(2.43%)
ECOG Performance(%) 0 1 2	10(24.38%) 28(68.29%) 03 (7.33%)	05(12.20%) 32(78.04%) 04 (9.76%)

Table II: Distribution of patients according to the requirement of feeding tube

Feeding tube	**Arm A (n=41) No. (%)**	**Arm B (n=41) No. (%)**	**P value**
Prior starting treatment	03(7.31%)	07(17.07%)	
During treatment	08(19.51%)	13(31.70%)	
Refused	02(4.82%)	01(2.43%)	0.232

Table III: Distribution of patients according to treatment compliance and delay

Variables	Arm A (n=41) No. (%)	Arm B (n=41) No. (%)	overall (n=82)	P value
Radiotherapy Completed within 45 days	25(60.97%)	31(75.60%)	56(68.29%)	
Delayed 1week	16(39.02%)	10(24.39%)	26(31.70%)	0.154
Chemotherapy				
5 cycle	02(4.87%)	00(0.0%)	02(2.43%)	
6 cycle	03(7.31%)	03(7.31%)	06(7.31%)	0.659
7 cycle	36(87.80%)	38(92.68%)	74(90.24%)	

Table IV: Clinical response at week 24 after completion of treatment

Response	Arm A (n = 41) No. (%)	Arm B (n=41) No. (%)	*P*-value
Complete response (CR)	29 (70.7%)	18 (43.9%)	
Partial response (PR)	04 (9.7%)	11 (26.8%)	
Stable disease (SD)	05 (12.2%)	04 (9.8%)	
Progressive disease (PD)	03 (7.4%)	08 (19.5%)	0.042

Table V: Distribution of patients according to acute toxicities

Toxicity	Grade	Arm A (n=41) No. (%)	Arm B (n=41) No. (%)	p- value
Oral mucositis	Grade 1	06 (14.6%)	10 (24.4%)	
	Grade 2	10 (24.4%)	11 (26.8%)	
	Grade 3	25 (61.0%)	20 (48.8%)	0.449
Xerostomia	Grade 0	00(0.0%)	01 (2.43%)	
	Grade 1	19 (46.34%)	22 (53.65%)	
	Grade 2	22 (53.66%)	18 (43.92%)	0.442
Dysphagia	Grade 1	19 (46.3%)	13 (31.7%)	
	Grade 2	11 (26.8%)	14 (34.1%)	
	Grade 3	08 (19.5%)	12 (29.2%)	0.478
Dysgeusia	Grade 1	23 (56.1%)	24 (58.5%)	
	Grade 2	09 (21.9%)	08 (19.5%)	
	Grade 3	00 (0.0%)	00 (0.0%)	0.961
Skin toxicity	Grade 1	15 (36.5%)	20 (48.7%)	
	Grade 2	19 (46.3%)	15 (36.5%)	
	Grade 3	06 (14.6%)	04 (09.7%)	0.590
Neutropenia	Grade 1	19(46.3%)	11 (26.8%)	
	Grade 2	08 (19.5%)	07 (17.0%)	
	Grade 3	03 (7.3%)	01 (2.4%)	0.662

Discussion

The role of induction chemotherapy remains questionable though several studies were carried out regarding the role of induction chemotherapy in locally advanced oropharyngeal cancers.[5] The aim of this study was to compare the effectiveness and toxicities of induction chemotherapy followed by concurrent chemoradiotherapy and concurrent chemoradiotherapy alone in inoperable locally advanced oropharyngeal cancers. Total 82 patients of inoperable locally advanced oropharyngeal squamous cell carcinoma were enrolled in this study from different centers of Bangladesh. After induction chemotherapy, CR was only in 12 (29.26%) and PR was in rest of the patients that correlates with Ghi et al., (2017) who found 32.1% patients had CR after induction chemotherapy.[17] During induction chemotherapy vomiting, diarrhea, nephrotoxicity and neutropenia were observed and managed accordingly. One patient developed febrile neutropenia for which he was admitted into

hospital and treated with full recovery. The concurrent radiotherapy was planned to be completed over 6.5 weeks (45 days). Majority of the patient tolerated the therapy well. The prolonged duration of radiotherapy schedule in Arm A more than Arm B corresponds to the higher amount of the grade 2 and grade 3 toxicities in Arm A for which the planned therapy were suspended till improvement. Bhattasali et al. (2018) also experienced that 27% of the patients in IC-CCRT arm and 18% patients in CCRT arm required treatment break.[18] Final follow up was given 24 weeks after completion of treatment. Treatment response was statistically significant between two groups ($p<0.05$).

This result correlates with Ghi et al., (2017) in terms of complete response which showed statistically significant complete response (42.5% versus 28%) in induction chemotherapy followed by CCRT group than CCRT alone group.[17]

During CCRT patients were assessed weekly for toxicity and after treatment as well. Both CT and RT related toxicities were observed during this period. Among them, oral mucositis, xerostomia, skin toxicity, dysphagia was frequently observed during this period. Feeding tube placement was planned in patients having >10% weight loss as compared to baseline, poor performance status, more than grade 2 mucositis and poor oral intake.

No patients were spared from mucositis. Grade 2 and grade 3 oral mucositis was higher in Arm A. But The difference was not statistically significant ($p>0.05$) which correlates with DE FELICE et al., (2016) where grade 3 mucositis was slightly higher (66.7% versus 50%) in induction followed by CCRT arm than CCRT alone arm.

Skin toxicity was observed within the radiation field in both the arms but more in Arm A. This difference was not statistically significant ($p>0.05$) which slightly differs with Ghi et al., (2017) where grade 3 skin toxicities were similar (14% versus 15%) between induction followed by CCRT and CCRT alone arms.[17] However more patients developed grade 3 in field dermatitis in CCRT alone arm in their study might be due to use of 5FU along with Cisplatin as concurrent chemotherapy.

Another most common and debilitating complication of radiotherapy is xerostomia which is caused by the radiation induced damage to the parotid and submandibular glands. Xerostomia was evaluated using patient's complaints and questionnaires weekly during radiotherapy as well as during follow up and no patient was spared from it.

Xerostomia was observed more in arm A but statistically insignificant ($p>0.05$) which correlates with DE FELICE et al., (2016) who found grade 1 and grade 2 xerostomia was similar (88.9% versus 72.2%) in both the arms.[9] However use of IMRT in their study might resulted in development of xerostomia in less number of patients.

Although the parotid gland is spared, not much consideration is given to preserve the pharyngeal constrictor muscles thus dysphagia has been reported as the major complication of the radiotherapy. Weekly dysphagia was recorded during radiotherapy and most of the patients of both arms suffered dysphagia of varying grade. More patients in arm A developed significant grade 2 and above dysphagia. However, the findings were statistically insignificant at 5% level. This might be due to higher incidence of dysphagia at primary presentation which was 29 (70.7%) in Arm A and 27 (65.8%) in Arm B. This findings support the study done by DE FELICE et al., (2016) who found more dysphagia in CCRT Arm than in IC–CCRT Arm (grade 3 dysphagia 22.2% in IC-CCRT arm versus 33.3% in CCRT arm).[9] However feeding tube requirement was more in arm B (see Table II) which correlates with the study done by Bhattasali et al (2018) where patients who received CCRT alone were more likely to require a feeding tube (57% vs 27%) compared to patients who received IC-CCRT.[18]

In A more patients had neutropenia which nearly correlates with DE FELICE et al., (2016) where grade 3 neutropenia was more in Arm A 11.1% vs and 5.6%.[9]

Other toxicities like nausea, vomiting, weight loss, dysgeusia, anemia, nephrotoxicity and

neurotoxicity were also observed between the two groups but no statistically significant differences were found (p>0.05). DE FELICE et al. (2016) also showed almost similar toxicities between two groups.[9]

Conclusion

In conclusion, the result of this study indicates that induction chemotherapy followed by concurrent chemoradiotherapy is more effective than concurrent chemoradiotherapy alone in terms of loco-regional control in inoperable locally advanced oropharyngeal squamous cell carcinoma with acceptable toxicities.

Competing Interests

There was no conflict of interest declared by the authors.

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