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INDUCTION CHEMOTHERAPY FOLLOWED BY CONCURRENT CHEMORADIOTHERAPY VERSUS CONCURRENT CHEMORADIOTHERAPY ALONE IN LOCALLY ADVANCED NASOPHARYNGEAL CANCER

Sajib Kumar Talukdhar[1]*, Sarwar Alam[2], Md. Abdul Bari[3], Md. Zillur Rahman Bhuiyan[4], Sadia Sharmin[5] and Md. Abdullah Al Maruf[6]

[1]Medical Officer, Department of Paediatrics, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh.
[2]Professor and Chairman, Department of Oncology, BSMMU, Dhaka, Bangladesh.
[3]Associate Professor, Department of Oncology, BSMMU, Dhaka, Bangladesh.
[4]Associate Professor, Department of Oncology, BSMMU, Dhaka, Bangladesh.
[5]Associate Professor, Department of Oncology, BSMMU, Dhaka, Bangladesh.
[6]Medical Officer, Upazilla Health Complex, Mehendiganj, Barishal, Bangladesh.

***Corresponding Author: Dr. Sajib Kumar Talukdhar**

Medical Officer, Department of Paediatrics, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh.

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ABSTRACT

Background: Concurrent chemoradiotherapy is the standard of care for patients with locally advanced nasopharyngeal carcinoma. Addition of induction chemotherapy remains unclear. **Objective:** The aim of this study was to compare the treatment response and toxicity of induction chemotherapy followed by concurrent chemoradiotherapy and concurrent chemoradiotherapy alone in locally advanced nasopharyngeal cancers. **Materials and Methods:** This quasi-experimental study was carried out among 80 patients of locally advanced squamous cell carcinoma of nasopharynx from June, 2018 to June, 2019. Who had fulfilled the inclusion and exclusion criteria were included and equally distributed into two treatment arms. Arm A received induction chemotherapy followed by concurrent chemoradiotherapy and Arm B received concurrent chemoradiotherapy alone. **Results:** Final responses were evaluated 3 months after the end of treatment. In Arm A, 27 (67.5%) patients showed complete response (CR) and in Arm B, CR was observed in 15 (37.5%) patients. Partial responses (PR) were 11 (27.5%) and 21 (52.5%) in two arms respectively. There were 02 (5.0%) progressive disease (PD) in Arm A and 04 (10.0%) PD in Arm B. Treatment responses were statistically significant between two groups (p-value=0.032). Toxic effects during chemoradiotherapy were almost similar in the two arms. **Conclusion:** Induction chemotherapy followed by concurrent chemoradiotherapy is more effective than concurrent chemoradiotherapy alone in locally advanced squamous cell carcinoma of nasopharynx with acceptable toxicities.

KEYWORDS: Nasopharyngeal cancer, Squamous cell carcinoma, Induction chemotherapy, Concurrent chemoradiotherapy.

INTRODUCTION

Head and neck cancers are the name given to a variety of malignant tumours and nasopharyngeal cancer is one of them.[1] The annual incidence of head and neck cancer world-wide is more than 887,000 cases (represents 5.2% of the total new cancer cases) with around 453,000 deaths each year. Among them, nasopharyngeal cancers were 129,079.[2] Regarding nasopharyngeal squamous cell carcinoma, WHO pathological classification includes three major types (keratinizing squamous cell carcinoma, non-keratinizing squamous cell carcinoma and basaloid squamous cell carcinoma).[3] The standard treatment of patients with locally advanced nasopharyngeal cancer is concurrent chemoradiotherapy (CCRT). Despite multimodality treatment, one-third of high-risk patients still experience recurrence, with distant metastasis as the primary failure.[4,5] Different strategies like addition of adjuvant and or induction chemotherapy were studied to improve outcome in patients with locally advanced nasopharyngeal cancer. The role of induction chemotherapy evaluated in several studies which revealed that induction chemotherapy before concurrent chemoradiotherapy have benefit in terms of locoregional control and survival.[6-9] Induction chemotherapy can serve as a predictive tool and allow for the appropriate selection of the subsequent definitive management strategy. Patients responding to induction chemotherapy are also those who respond best to radiotherapy.[10] In our study, we used cisplatin plus fluorouracil as induction schedule as it is convenient, feasible and well tolerated. The main goal of this study was to compare the treatment response and toxicity of induction chemotherapy

followed by concurrent chemoradiotherapy and concurrent chemoradiotherapy alone in locally advanced nasopharyngeal cancers in terms of locoregional control.

MATERIALS AND METHODS

This was a quasi-experimental study carried out among 80 patients of locally advanced squamous cell carcinoma of nasopharynx from June, 2018 to June, 2019 at Department of Oncology, Bangabandhu Sheikh Mujib Medical University (BSMMU) and Department of Radiotherapy, National Institute of Cancer Research and Hospital (NICRH), Dhaka. Ethical approval was taken from the Institutional Review Board (IRB) of BSMMU on 28 may 2018. Patients aged ≥ 18 years were eligible if they had Stage III/IVA locally advanced Squamous cell carcinoma of nasopharynx; Eastern Co-operative Oncology Group (ECOG) performance status score zero to two; no prior chemotherapy or radiotherapy or surgery. After selection of patients, a written informed consent was taken from each patient before his or her participation in this study. Who had fulfilled the inclusion and exclusion criteria were included and equally distributed into two treatment Arms. Arm A received induction chemotherapy followed by concurrent chemoradiotherapy and Arm B received concurrent chemoradiotherapy alone. Induction chemotherapy was given in Arm A only. Injection cisplatin 100mg/m2 IV on day 1 and injection 5-FU 1000mg/m2/day IV continuous infusion on day 1 to day 5(3 weekly cycle for 3 cycles).[11] Proper hydration was done. Pre and post chemotherapy medication with anti-emetic, steroid and other necessary drugs were given before and after chemotherapy. Both arm A and arm B got concurrent chemoradiotherapy. Radiotherapy dose was 66 Gray in 33 daily fractions, 2 Gray per day in two equal divided doses (1 Gray each in each field) were delivered from both side of the neck, five days in a week over 6.5 weeks for both arm A and arm B. Both arms were received concurrent chemotherapy during whole length of radiotherapy period by weekly cisplatin 30mg/m2 starting from first day of radiotherapy.[12] Patients were assessed three weekly during induction chemotherapy and weekly during concurrent chemoradiotherapy. Tumour response was evaluated according to the WHO guideline of responses (RECIST criteria). To assess toxicity, The National Cancer Institute's "Common Terminology Criteria for Adverse Events, v.3.0" published on June 10, 2003 was used. They were also evaluated at 6 and 12 weeks after completion of treatment. During follow-up toxicities and tumour response were assessed by clinical examination and relevant investigations. The final response was assessed after clinical examination, CT scan of the head and neck with contrast, chest X-ray P/A view, USG of whole abdomen and nasopharyngoscopy. Data analysis was done according to the objectives of the study by using the SPSS (Statistical Package for Social Science) software program for windows, version 13.0 available in the institute. To prevent bias, lost to follow up patients were included. Difference between two means was assessed by t-test. All outcomes were compared by chi-square test. Fisher's Exact test was done when more than 20 percent of cells in the cross table had expected frequency less than 5. A p-value of less than 0.05 in two-tailed test as considered as statistically significant.

RESULTS

The total study population was 80 among which 40 were in Arm A and 40 in Arm B. The mean age of Arm A and Arm B patients were 52.23 (±12.21) years and 54.05 (±11.47) years respectively. Male and female ratio was 2:1. Most of the patients in both Arms shows ECOG score of 1 (52.50% in Arm A and 45.0% in Arm B). 32.5.2% patients of Arm A and 37.5% patients of Arm B were in stage III and 67.5% patients of Arm A and 62.5% patients of Arm B were in stage IVA.

Table 1: Patients characteristics.

Characteristics		Arm A(n=40)	Arm B(n=40)
Age	Mean±SD (years)	52.23 (±12.21)	54.05 (±11.47)
Sex	Male	26(65.0%)	27(67.5%)
	Female	14(35%)	13(32.5%)
Clinical stage	Stage III	13(32.5%)	15(37.5%)
	Stage IVA	27(67.5%)	25(62.5%)
ECOG performance	0	15(37.5%)	17(42.5%)
	1	21(52.5%)	18(45.0%)
	2	04(10.0%)	05(12.5%)

Responses were assessed at final follow up after 3 months of treatment. In Arm A, 27 (67.5%) patients showed complete response (CR) and in Arm B, CR was observed in 15 (37.5%) patients. Partial responses (PR) were 11 (27.5%) and 21 (52.5%%) in two arms respectively. Treatment response was statistically significant between two groups (p=0.032).

Table 2: Responses at final follow-up (at 3 months) after completion of treatment for both Arm A and Arm B.

Responses	Arm A(n=40)	Arm B(n=40)	p-value
Complete response	27(67.5%)	15(37.5%)	0.032
Partial response	11(27.5%)	21(52.5%)	
Progressive disease	02(05.0%)	04(10.0%)	

Oral mucositis, skin toxicity, xerostomia, neutropenia and nephrotoxicity were frequently observed during concurrent chemoradiotherapy. No grade 4 toxicity was observed. Grade 3 toxicities were more in Arm A than Arm B but not statistically significant.

Table 3: Distribution of patients by common toxicities.

Toxicities		Arm A(n=40)	Arm B(n=40)	p-value
Oral mucositis	Grade1	21(52.5%)	25(62.5%)	0.479
	Grade2	16(40.0%)	14(35.0%)	
	Grade3	03(07.5%)	01(02.5%)	
Skin toxicity	Grade1	24(60.0%)	21(52.5%)	0.638
	Grade2	14(35.0%)	15(37.5%)	
	Grade3	02(05.0%)	04(10.0%)	
Xerostomia	Grade1	28(70.0%)	24(60.0%)	0.348
	Grade2	12(30.0%)	16(40.0%)	
Neutropenia	Grade1	12(30.0%)	14(35.0%)	0.587
	Grade2	07(17.5%)	05(12.5%)	
	Grade3	04(10.0%)	02(05.0%)	
Nephrotoxicity	Grade1	14(35.0%)	16(40.0%)	0.543
	Grade2	05(12.5%)	04(10.0%)	
	Grade3	03(07.5%)	01(02.5%)	

DISCUSSION

The standard treatment of patients with locally advanced nasopharyngeal cancer is chemoradiotherapy. The role of induction chemotherapy remains controversial. Several studies were carried out regarding the role of induction chemotherapy in locally advanced nasopharyngeal cancers. Among them, some showed that Induction Chemotherapy before concurrent chemoradiotherapy increases overall survival, progression free survival, disease free survival and locoregional control.[6-9] The aim of this study was to compare the treatment response and toxicity of induction chemotherapy followed by concurrent chemoradiotherapy and concurrent chemoradiotherapy alone in locally advanced nasopharyngeal cancers.

Diagnosed patients of locally advanced nasopharyngeal squamous cell cancers were enrolled in this study. Final follow up was given 3 months after completion of treatment. In Arm A, 27 (67.5%) patients showed complete response (CR) and in Arm B, CR was observed in 15 (37.5%) patients. Partial responses (PR) were 11 (27.5%) and 21 (52.5%) in two arms respectively. There were 02 (5.0%) progressive disease (PD) in Arm A and 04 (10.0%) PD in Arm B. Treatment responses were statistically significant between two groups (p-value=0.032). This result correlates with Kaval et al. which showed that locoregionally advanced nasopharyngeal cancer patients treated with induction chemotherapy followed by concurrent chemoradiotherapy have a high locoregional control rate.[9]

During concurrent chemoradiotherapy patients were assessed weekly for toxicity and after treatment as well. Both chemotherapy and radiotherapy related toxicities were observed during this period. Among them, oral mucositis, skin toxicity and xerostomia were frequently observed during this period. In Arm A, 03 (7.5%) patients developed grade 3 oral mucositis and in Arm B, 01 (2.5%) patients developed grade 3 oral mucositis. Skin toxicity was observed in the radiation field in both arms. In Arm A, 02 (5.0%) patients developed grade 3 Skin toxicity and in Arm B, 04 (10.0%) patients developed grade 3 Skin toxicity. In respect of neutropenia, 04 (10.0%) patients in arm A and 02 (5.0%) in arm B showed grade 3. Xerostomia was a common complication of Radiotherapy and no patient was spared from it. In Arm A, 28 (70.0%) and 12 (30.0%) patients had suffered from grade1 and 2 toxicity respectively and In Arm B, 24 (60.0%) and 16 (40.0%) patients had suffered from grade1 and 2 toxicity respectively. These differences were not statistically significant ($p>0.05$). A meta-analysis of randomized controlled trials showed Patients treated with induction chemotherapy and CCRT had higher incidence of grade 3–4 neutropenia than patients treated with CCRT alone. That meta-analysis also found no significant difference in other grade 3–4 adverse events and radiation toxicity between the two groups.[8] In our study, we also found more grade3 neutropenia in induction arm (Arm A) but result was not statistically significant. However, toxicities were well tolerated and manageable. From these findings it can be said that induction chemotherapy followed by concurrent chemoradiotherapy is more effective in terms of loco-regional control.

CONCLUSION

In conclusion, the result of this study indicates that induction chemotherapy followed by concurrent chemoradiotherapy is more effective than concurrent chemoradiotherapy alone in locally advanced squamous cell carcinoma of nasopharynx with acceptable toxicities.

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