Research Article

A prospective study of response and toxicity of induction chemotherapy followed by concurrent chemoradiation versus only concurrent chemoradiation in patients with locoregionally advanced unresectable head-and-neck cancer

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ABSTRACT

Background: The first-line treatment for locally advanced squamous cell carcinoma of head-and-neck cancer is concurrent chemoradiation, which is the standard of care. Concurrent chemoradiation improved locoregional control but little impact on distance metastases. Induction chemotherapy (IC) can reduce local disease and distance metastases. **Objectives:** The purpose of our study is to compare the outcome of disease and toxicity between IC followed by concurrent chemo-radiation and only concurrent chemoradiation in patients of locally advanced unresectable head-and-neck cancer. **Materials and Methods:** A total of 37 patients were included in IC followed by concurrent chemoradiotherapy group. IC was administered with injection paclitaxel, injection carboplatin, and injection 5-fluorouracil for three cycles. Thirty-six patients were included in Arm B, concurrent chemoradiation group. The total dose of radiation was given in both the Arms 66 Gy in 33 fractions, five fractions per week for 6.3 weeks with concurrent chemotherapy injection cisplatin 40 mg/m^2 weekly. **Results:** Grade 4 skin reaction was 2 (7%) in Arm A and 1 (3.3%) in Arm B. Grade 3 febrile neutropenia was 1 (3.4%) in Arm A and no Grade 3 febrile neutropenia was seen in Arm B. Grade 3 thrombocytopenia was 1 (3.4%) in Arm A and 2 (6.6%) in Arm B. Complete response of disease after 6 months of completion of treatment was 19 (65.5%) in Arm A and 18 (60%) in Arm B. **Conclusion:** Our study showed no significant difference in disease response regarding locoregional disease control between two groups but distance recurrence can be reduced with IC with manageable toxicity.

KEY WORDS: Induction Chemotherapy; Concurrent Chemoradiotherapy; Head-and-Neck Cancer

INTRODUCTION

Head-and-neck cancers affect the upper aerodigestive tract and are one of the most common cancers worldwide. [1] With 77,000 cases diagnosed per year, head-and-neck cancer is the second most common cancers in the Indian population.[2] While smoked tobacco and alcohol are the major causative factors for head-and neck-cancers worldwide, smokeless tobacco, betel nut, and Epstein–Barr virus are etiological agents responsible for it in the Asian population.[3] The majority of head-and-neck cancers patients present with locoregionally advanced disease at the time of diagnosis. The treatment of head-and-neck cancers has a multimodality concept and multi-disciplinary approach include surgery, radiotherapy, concurrent chemoradiation (CCRT). In many trials, chemotherapy had been used as CCRT, induction chemotherapy (IC), and adjuvant chemotherapy after radiotherapy. The first-line treatment

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for Stages III and IV disease is concurrent chemoradiation which is the standard of care. In the advanced stage of disease treated with surgery and radiotherapy 40–60% of patients showed relapse and 30–50% of patients live for 3 years.[4,5] Concurrent chemoradiation improved locoregional control but little impact on distance metastases. IC can reduce local disease and distance metastases,[6] helps organ preservation also.[4] IC with cisplatin showed response rate 80–90%, with complete response rate was 20–40%.[7] The purpose of our study is to compare outcome of disease and toxicity between IC followed by concurrent chemoradiation and only concurrent chemoradiation in patients of locally advanced head-and-neck cancer.

MATERIALS AND METHODS

A total of 73 patients were included in our study and the study was done at the Department of Radiotherapy, Nilratan Sarkar Medical College and Hospital, Kolkata, between January 2016 and December 2017. Histopathologically squamous cell carcinoma proved locally advanced head-and-neck cancer, unresectable, non-metastatic, without previous surgery, radiotherapy, and chemotherapy were included in our study. The sites of primary lesion were oral cavity, oropharynx, hypopharynx, and larynx. Performance status of the patients was as per Eastern Cooperative Oncology Group (ECOG) 0–1. Investigations were done biopsy for histopathology type, complete blood count, liver function test, urea, creatinine, sugar fasting and PP, computed tomography (CT) scan, magnetic resonance imaging (MRI) of face and neck, indirect laryngoscopy, nasal endoscopy, fiber optic laryngoscopy, Chest X-ray posteroanterior view, and CT scan of chest if indicated.

A total of 37 patients were included in Arm A, IC followed by CCRT (IC+CCRT) group. IC was administered with injection paclitaxel 175 mg/m^2 in 500 ml normal saline (glass bottle) over 3 h, injection carboplatin area under the curve 6 in 5% dextrose solution over 1 h and injection 5 fluorouracil 1000 mg/m^2 continuous infusion for 3 days (D1–D3). Before chemotherapy pre-medications were given as per guideline. IC had been given 3 weekly interval for three cycles. Supportive therapy including blood transfusion (to keep hemoglobin >10 g%), injection pegfilgrastim 6 mg subcutaneously on day D4, tablet ciprofloxacin 500 mg twice daily for 5 days as prophylaxis, and platelet transfusion was given when required. In Arm A, concurrent chemoradiation with injection cisplatin 40 mg/m^2 weekly was started after three cycles of IC. Thirty-six patients were included in Arm B, concurrent chemoradiation (CCRT) group and patients received injection cisplatin 40 mg/m^2 weekly during radiation. Total dose of radiation was given in both the Arms 66 Gy in 33 fractions, five fractions per week for 6.3 weeks. Cobalt 60 teletherapy machine was used for radiation treatment. During radiation, patients were followed up weekly. Treatment-related toxicity was assessed through the National Cancer Institute Common Toxicity Criteria v4.0. Disease response was assessed through the Response Evaluation Criteria in Solid Tumors v1.1.[8] Disease response was assessed clinically, CT scan, MRI at the end of IC and completion of radiotherapy and during follow-up.

RESULTS

Seventy-three patients of head-and neck-cancer Stages III, IVA, and IVB met the inclusion and exclusion criteria were included in our study. Thirty-seven patients were included in Arm A, IC+CCRT group and 36 patients were included in Arm B, only concurrent chemoradiation group. The patient characteristics were well balanced in both the Arms and are shown in Table 1. The median age of the patient was in Arm A 56 years and Arm B 57 years. The male patients were 30 (81%) in Arm A and 31 (86%) in Arm B. The female patients were 7 (19%) in Arm A and 5 (14%) in Arm B. Most of the patients had tobacco habits. In both the Arms, performance status (ECOG) was 0–1. Most of the patients had performance status (ECOG) 1, 24 (65%) in Arm A and 22 (61%). Most of the patients had primary disease site at oropharynx, 14 (38%) in Arm A and 14 (39%) in Arm B. Most of the patients in both the groups had Stages IVA and IVB, 25 (68%) in Arm A and 23 (64%) in Arm B.

Three patients in Arm A did not come after two cycles of IC and 34 patients completed IC. Toxicities developed during IC in Arm A, as shown in Table 2. Grade 3 vomiting was 3 (8.8%). Oral mucositis Grade 3 was 3 (8.8%) and Grade 4 was 2 (5.9%). Grade 3 diarrhea was 2 (5.8%). Grade ½ neurotoxicity was 6 (17.6%). Paclitaxel induced myalgia and arthralgia Grade 3 was 3 (8.8%). Grade ½ anemia was

Table 1: Patients characteristics

Characteristics	Arm A (*n*=37) (IC+CCRT) (%)	Arm B (*n*=36) (CCRT) (%)
Median age (years)	56	57
Sex (%)		
Male	30 (81)	31 (86)
Female	7 (19)	5 (14)
Tobacco habits (%)	35 (94.6)	33 (91.6)
Performance score (ECOG) (%)		
0	13 (35)	14 (39)
1	24 (65)	22 (61)
Primary disease sites (%)		
Oral cavity	6 (16)	5 (14)
Oropharynx	14 (38)	14 (39)
Hypopharynx	8 (22)	7 (19)
Larynx	9 (24)	10 (28)
Stage of disease (American Joint Committee on Cancer 7th edition) (%)		
III	12 (32)	13 (36)
IV A and B	25 (68)	23 (64)

ECOG: Eastern Cooperative Oncology Group

9 (26.4%) and Grade 4 was 1 (2.9%). Neutropenia grade was 3 (8.8%) and Grade 4 was 1 (2.9%). Grade 3 febrile neutropenia was 2 (5.9%) and Grade 3 thrombocytopenia was 2 (5.9%).

In Arm A, two patients did not come after 2 weeks of chemoradiation treatment, three patients did not come after 3 weeks of concurrent chemoradiation treatment and 29 patients completed chemoradiation treatment. In Arm B, three patients did not come after 2 weeks and three patients did not come after 3 weeks of concurrent chemoradiation treatment and 30 patients completed concurrent chemoradiation treatment. Toxicities developed during concurrent chemoradiation treatment in both the Arms, as shown in Table 3. Grade 3 vomiting was 5 (17.2%) in Arm A and 3 (10%) in Arm B. Grade 3 mucositis was 12 (41.3%) in Arm A and 11 (36.6%) in Arm B and Grade 4 mucositis was 1 (3.4%) in Arm A and 1 (3.3%) in Arm B. Grade 3 dysphagia was 4 (13.8%) in Arm A and 3 (10%) in Arm B. Grade 4 skin reaction was 2 (7%) in Arm A and 1 (3.3%) in Arm B. Grade ½ neurotoxicity was 1 (3.4%) in Arm A and 1 (3.3%) in Arm B. Grade 3 and Grade 4 anemia was 4 (13.7%), 1 (3.4%) in Arm A and 3 (10%), 0% in Arm B, respectively. Grade 3 neutropenia was 3 (10.3%) in Arm A and 2 (6.6%) in Arm B. Grade 3 febrile neutropenia was 1 (3.4%) in Arm A and no Grade 3 febrile neutropenia was seen in Arm B. Grade 3 thrombocytopenia was 1 (3.4%) in Arm A and 2 (6.6%) in Arm B.

Table 2: Toxicities developed during induction chemotherapy in Arm A (*n*=34)

Toxicities	Grade 1/2 (%)	Grade 3 (%)	Grade 4 (%)
Non-hematological toxicities			
Vomiting	6 (17.6)	3 (8.8)	0
Oral mucositis	8 (23.5)	3 (8.8)	2 (5.9)
Diarrhea	6 (17.6)	2 (5.8)	0
Dysphagia	5 (14.7)	0	0
Neurotoxicity	6 (17.6)	0	0
Ototoxicity	0	0	0
Nephrotoxicity	0	0	0
Myalgia and arthralgia	12 (35.3)	3 (8.8)	0
Hematological toxicities			
Anemia	9 (26.4)	1 (2.9)	0
Neutropenia	8 (23.5)	3 (8.8)	1 (2.9)
Febrile neutropenia	5 (14.7)	2 (5.9)	0
Thrombocytopenia	3 (8.8)	2 (5.9)	0

At 2 months of completion of treatment complete response was 13 (44.8%) in Arm A and 12 (40%) in Arm B [Table 4]. Partial response was 12 (41.3%) in Arm A and 13 (43.3%) in Arm B. Stable disease was 2 (6.8%) in Arm A and 2 (6.6%) in Arm B. Progressive disease was 2 (6.8%) in Arm A and 3 (10%) in Arm B.

At 6 months of completion of treatment complete response was 19 (65.5%) in Arm A and 18 (60%) in Arm B [Table 5]. Partial response was 6 (20.6%) in Arm A and 7 (23.3%) in Arm B. Stable disease was 2 (6.8%) in Arm A and 2 (6.6%) in Arm B. 2 (6.6%) patients developed distant metastases in Arm B and no metastases in Arm A.

DISCUSSION

The median age of the patient was in Arm A 56 years and Arm B 57 years. Most of the patients had primary disease site at oropharynx, 14 (38%) in Arm A and 14 (39%) in Arm B. Most of the patients in both the groups had Stages

Table 3: Toxicities developed during concurrent chemoradiation

Toxicities	Arm A (*n*=29) (%)			Arm B (*n*=30) (%)		
	G1/2	G3	G4s	G1/2	G3	G4
Non-hematological						
Vomiting	10 (34.4)	5 (17.2)	0	12 (40)	3 (10)	0
Oral mucositis	16 (55.1)	12 (41.3)	1 (3.4)	18 (60)	11 (36.6)	1 (3.3)
Diarrhea	5 (17.2)	0	0	6 (20)	0	0
Dysphagia	25 (86.2)	4 (13.8)	0	27 (90)	3 (10)	0
Skin reaction	18 (62)	9 (31)	2 (7)	19 (63.3)	10 (33.3)	1 (3.3)
Neurotoxicity	1 (3.4)	0	0	1 (3.3)	0	0
Ototoxicity	0	0	0	0	0	0
Nephrotoxicity	4 (13.7)	0	0	3 (10)	0	0
Hematological						
Anemia	12 (41.4)	4 (13.7)	1 (3.4)	9 (30)	3 (10)	0
Neutropenia	10 (34.4)	3 (10.3)	0	8 (26.6)	2 (6.6)	0
Febrile neutropenia	5 (17.2)	1 (3.4)	0	4 (13.3)	0	0
Thrombocytopenia	5 (17.2)	1 (3.4)	0	4 (13.3)	2 (6.6)	0

Table 4: Disease response at 2 months of completion of treatment

Disease response	Arm A (*n*=29) (IC+CCRT) (%)	Arm B (*n*=30) (CTRT) (%)
Complete response	13 (44.8)	12 (40)
Partial response	12 (41.3)	13 (43.3)
Stable disease	2 (6.8)	2 (6.6)
Progressive disease	2 (6.8)	3 (10)

Table 5: Disease response at 6 months of completion of treatment

Disease response	Arm A (*n*=29) (IC+CCRT) (%)	Arm B (*n*=30) (CTRT only) (%)
Complete response	19 (65.5)	18 (60)
Partial response	6 (20.6)	7 (23.3)
Stable disease	2 (6.8)	2 (6.6)
Distant metastasis	0	2 (6.6)

IVA and IVB, 25 (68%) in Arm A and 23 (64%) in Arm B. During IC, Grade 3 vomiting was 3 (8.8%), paclitaxel-induced myalgia Grade 3 was 3 (8.8%), Grade 4 anemia was 1 (2.9%), and Grade 3 febrile neutropenia was 2 (5.9%). During concurrent chemoradiation grade, Grade 4 mucositis was 1 (3.4%) in Arm A and 1 (3.3%) in Arm B. Grade 4 skin reaction was 2 (7%) in Arm A and 1 (3.3%) in Arm B. Grade 4 anemia was 1 (3.4%) in Arm A and 0% in Arm B. Grade 3 thrombocytopenia was 1 (3.4%) in Arm A and 2 (6.6%) in Arm B. At 2 months of the completion of treatment complete response was 14 (48.2%) in Arm A and 9 (30%) in Arm B. At 6 months of completion of treatment complete response was 18 (72%) in Arm A and 14 (56%) in Arm B. One patient developed distant metastases in Arm B.

Paccagnella *et al*.[9] reported in their study that the median age was 58 year in the docetaxel, cisplatin, 5-fluorouracil (TPF) plus chemoradiotherapy group and 60 years in the chemoradiotherapy alone group, oral cavity/oropharynx was the primary tumor site in 70% of patients in the TPF plus chemoradiotherapy group and 71% of patients in the chemoradiotherapy alone group and the majority had Stage IV cancer 84% in TPF plus chemoradiotherapy group and 82% in chemoradiotherapy alone group. Hitt *et al*.[10] reported in their study that the median age was 58.1 years in TPF-CCRT group, 57.5 years in cisplatin, 5-fluorouracil (PF)-CCRT group, and 56.5 years in CCRT group, the majority of the patients had primary site was oropharynx 66 (42.6%) in TPF-CCRT group, 67 (43%) in PF-CCRT group, and 54 (42.2%) in CCRT group. In our study, the median age of the patient was 56 years in Arm A and 57 years in Arm B, most of the patients had primary disease site at oropharynx, 14 (38%) in Arm A and 14 (39%) in Arm B, most of the patients in both the groups had Stages IVA and IVB, 25 (68%) in Arm A and 23 (64%) in Arm B.

Paccagnella *et al*.[9] reported in their study that during induction TPF, the most frequent Grades 3 or 4 non-hematologic toxicities were nausea (4%) and stomatitis (6%) and the most frequent Grades 3 or 4 hematologic toxicities were neutropenia (52%) and febrile neutropenia (8%). Hitt *et al*.[10] reported toxicities during IC in their study that Grade 3 stomatitis was 12 (7.8%) in TPF group, 18 (11.5%) in PF group and Grade 4 stomatitis was 2 (1.3%) in TPF group, and 5 (3.2%) in PF group. The Grade 3 vomiting was 9 (5.9%) in the TPF group and 3 (1.9%) in PF group. The hematological toxicity was Grade 3 anemia 3 (2%) and Grade 4 anemia 1 (0.7%) in the TPF group, Grade 3 anemia 1 (0.6%) in PF group. Neutropenia was 9 (5.9%) Grade 3, 20 (13.1%) Grade 4 in TPF group and 41 (26.3%) Grade 3, 13 (8.3%) Grade 4 in PF group. In TPF group, febrile neutropenia Grade 3 was 6 (3.9%) and Grade 4 was 20 (13.1%); and in PF group, febrile neutropenia Grade 3 was 1 (0.6%) and Grade 4 was 2 (1.3%). Cohen *et al*.[11] reported toxicity during IC in their study that there was Grade ¾ nausea/vomiting 8/136, mucositis 21/136, anemia 1/136, and neutropenia 15/136. In our study, toxicities developed during IC Grade 3 vomiting was 3 (8.8%), oral mucositis Grade 3 was 3 (8.8%), and Grade 4 was 2 (5.9%), paclitaxel-induced myalgia and arthralgia Grade 3 was 3 (8.8%). Grade 4 anemia was 1 (2.9%). Neutropenia Grade 4 was 1 (2.9%), Grade 3 febrile neutropenia was 2 (5.9%), and Grade 3 thrombocytopenia was 2 (5.9%).

Chen *et al*.[12] reported in their study regarding Grade ¾ toxicities during concurrent chemoradiation that mucositis was 19/60 in IC followed by concurrent chemoradiation group (IC+CCRT) and 18/60 in only concurrent chemoradiation group (CCRT), skin reaction was 10/60 in IC+CCRT group and 9/60 in CCRT group, anemia was 3/60 versus 1/60 in IC+CCRT versus CCRT group, neutropenia 5/60 versus 6/60 in IC+CCRT group versus CCRT group, respectively. Haddad *et al*.[13] showed in their study that febrile neutropenia was 16/70 versus 1/75 in IC+CCRT group versus CCRT group respectively, mucositis was 33/70 versus 12/75 in IC+CCRT group versus CCRT, respectively. Paccagnella *et al*.[9] reported in their study that Grade ¾ toxicities in IC+CCRT group versus CCRT were mucositis 12/43 versus 18/49, skin reaction 8/43 versus 6/49, dysphagia 9/43 versus 10/49, anemia 2/43 versus 0/49, neutropenia 2/43 versus 4/49, and thrombocytopenia 2/43 versus 2/49 in IC+CCRT versus CCRT , respectively. In our study, Grade 3 vomiting was 5 (17.2%) in Arm A and 3 (10%) in Arm B. Grade 3 mucositis was 12 (41.3%) in Arm A and 11 (36.6%) in Arm B and Grade 4 mucositis was 1 (3.4%) in Arm A and 1 (3.3%) in Arm B. Grade 3 dysphagia was 4 (13.8%) in Arm A and 3 (10%) in Arm B. Grade 4 skin reaction was 2 (7%) in Arm A and 1 (3.3%) in Arm B. Grade ½ neurotoxicity was 1 (3.4%) in Arm A and 1 (3.3%) in Arm B. Grade 3 and Grade 4 anemia was 4 (13.7%), 1 (3.4%) in Arm A and 3 (10%), 0% in Arm B, respectively. Grade 3 febrile neutropenia was 1 (3.4%) in Arm A and no Grade 3 febrile neutropenia was seen in Arm

B. Grade 3 thrombocytopenia was 1 (3.4%) in Arm A and 2 (6.6%) in Arm B.

Paccagnella *et al*.[9] reported that complete response at 6–8 weeks was 23 (50%) in TPF + CRT group and 10 (21%) in CRT group, partial response was 13 (28%) in TPF + CRT group and 29 (62%) in CRT group, progressive disease was 9 (20%) in TPF + CRT group and 8 (17%) in CRT group. At 8 months completion of treatment complete response was 57% in TPF + CRT group and 40% in CRT group. In our study, at 2 months of completion of treatment complete response was 13 (44.8%) in Arm A and 12 (40%) in Arm B [Table 4]. Partial response was 12 (41.3%) in Arm A and 13 (43.3%) in Arm B. Stable disease was 2 (6.8%) in Arm A and 2 (6.6%) in Arm B. Progressive disease was 2 (6.8%) in Arm A and 3 (10%) in Arm B. At 6 months of completion of treatment complete response was 19 (65.5%) in Arm A and 18 (60%) in Arm B [Table 5]. Partial response was 6 (20.6%) in Arm A and 7 (23.3%) in Arm B. Stable disease was 2 (6.8%) in Arm A and 2 (6.6%) in Arm B. 2 (6.6%) patients developed distant metastases in Arm B and no metastases in Arm A.

The major limitation of our study was a small sample size and short duration of follow-up. Hence, overall survival, disease-free survival or progression-free survival and late radiation-induced toxicity could not be assessed. A large number of cases and long duration follow-up are necessary to achieve more accurate results.

CONCLUSION

From our study, we could not find any significant difference in disease response between the two groups. Only distant relapse can be reduced by IC. IC group also showed an increased incidence of manageable acute toxicity. A large number of cases and long duration follow-up is necessary to achieve more accurate results and to comment on overall survival and progression-free survival.

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