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Original Article

Induction with Taxane/Platinum Based/5-Fu (TPF) Chemotherapy as a Predictor of Response to Definitive Concurrent Chemo Radiotherapy (CCRT) in Locally Advanced Inoperable Head and Neck Cancers

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ABSTRACT

Objective: To evaluate the effect of induction with Taxane/platinum based/5-FU chemotherapy as a predictor of response to definitive concurrent chemoradiotherapy in inoperable locally advanced squamous cell carcinoma of head and neck.

Study Design: Interventional study.

Place and Duration of Study: Medical Oncology Department, Jinnah Postgraduate Medical Center Karachi, Pakistan, from Oct 2019 to Oct 2020.

Methodology: A total of 71 patients aged 18 years or more with inoperable, locally advanced squamous cell carcinoma of the head and neck were included. Patients were given three cycles of induction therapy with injection Docetaxel 75 mg/m^2 day 01, injection Cisplatin 75 mg/m^2 intravenously (IV) day 01 and 5-Fluorouracil 1000 mg/m^2 IV day one-four every three weeks. CT scan was repeated after the last cycle to check response. All patients irrespective of response to induction received concurrent chemoradiotherapy, which included administration of weekly Carboplatin AUC-2 with radiotherapy 5 days per week. Response was assessed according to revised Response Evaluation Criteria in Solid Tumors (RECIST v1.0) criteria.

Results: The mean age of our respondents was 48.46±12.74 years. Of 71 patients, 26(36.6%) had achieved partial response after concurrent chemoradiotherapy, 24(33.8%) had achieved complete response, 10(14.1%) had stable disease and 11(15.5%) had progressive disease. There was a statistically significant association between response to concurrent chemoradiotherapy and response to induction chemotherapy (p=0.001).

Conclusion: The response of induction chemotherapy can be used as a guide to select patients for definitive concurrent chemoradiotherapy versus palliative treatment.

Keywords: Chemoradiotherapy, Head and Neck Carcinomas, Induction Chemotherapy, Squamous Cell Carcinoma of Head and Neck.

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INTRODUCTION

Head and neck cancer (HNC) is the 18th most frequent malignancy with an estimated incidence of 830,000 cases and 430,000 deaths worldwide.[1] Squamous cell carcinomas (SCC) arising from the mucosal surface of the oral cavity, nasopharynx, hypopharynx, oropharynx, and larynx, comprise about 90% of HNCs.[2] There are significant regional variations in the anatomic distribution and prevalence of HNCs worldwide, largely due to behavioral variations in the use of cigarettes, tobacco, betel nuts and alcohol, which lead to 80% of HNCs worldwide. Oral squamous cell carcinoma (OSCC) is the most common cancer in males and the third most common in females in high-risk countries such as Pakistan, Sri Lanka, India and Bangladesh.[1,2]

About 75% of patients with SCC are at an advanced stage of the disease (stage III or IV) and have a poor prognosis.[3] Multimodal treatment, such as resection along with radiation therapy or concurrent chemoradiotherapy, is typically used in these patients. These therapies are strongly contingent on the histology, grade, or metastasis of the regional lymph node.[3,4] Concurrent chemoradiotherapy (CCRT) has demonstrated positive outcomes, which offers 8% of the five-year survival benefit for head and neck cancer patients.[4]

Induction chemotherapy (ICT) has a significant part in preservation of organs and in decreasing treatment failure, though its ability to extend overall survival has not been proved.[5] A meta-analysis of Chemotherapy in Head and Neck Cancer (MACH-NC) revealed that ICT Cisplatin/5-Fluorouracil accompanied by local therapy was associated with an increase in overall survival.[6] In recent MACH-NC updates, Cisplatin/5-Fluorouracil plus Taxane (TPF) has improved progression-free as well as overall

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survival, compared to Cisplatin/5-Fluorouracil alone.[7,8]

The aim of the present study was to assess the response of induction with TPF chemotherapy as a predictor of response to definitive CCRT in the inoperable locally advanced squamous cell carcinoma of head and neck (ILASCCHN).

METHODOLOGY

This interventional study was carried out at the Medical Oncology Department, Jinnah Postgraduate Medical Center, Karachi, Pakistan from Oct 2019 to Oct 2020, after obtaining ethical approval from the Institutional Ethical Review Committee (ERC No. F-21-81-IRB/2019-GENL/32731/JPMC).

Inclusion Criteria: Patients of either gender aged 18 years or more with inoperable, locally advanced squamous cell carcinoma of head and neck (stage III-IV) with no distant metastasis were included.

Exclusion Criteria: Patients with any histology other than SCC, SCC of lips, a history of prior chemo-radiation, documented medication hypersensitivity and Eastern Cooperative Oncology Group (ECOG) performance status 3 were excluded from the study.

Decision regarding the unresectability for radical surgery was made by a multidisciplinary team, which included a surgeon, a radiation oncologist, a medical oncologist and a radiologist. Inoperability criteria were patient unfit for surgery due to medical reasons, unresectable disease deemed by surgeon or patient not willing for surgery due to organ preservation or to avoid surgical morbidity.

OpenEpi sample size calculator was used to estimate sample size, using statistics of overall ICT response as 76%,[5] which came to 71. Patients were recruited using non-probability convenience sampling.

After obtaining written, informed consent, data regarding socio-demographics (like age, gender, residence, occupation, ethnicity, addictions and family history), comorbid conditions and clinical findings were collected from all patients. Initially, the stage of tumor was assessed on CT scan. Patients with Locally Advanced Head and Neck Squamous Cell Carcinoma (LAHNSCC) were given three cycles of induction chemotherapy with injection Docetaxel 75 mg/m^2 day one, injection Cisplatin 75 mg/m^2 IV day one and 5-FU 1000 mg/m^2 IV day one to day four every three weeks. Those who developed neutropenia in the first cycle were given Granulocyte Colony Stimulating Factor (G-CSF) support in subsequent cycles. CT scan imaging was repeated after 3 weeks of last cycle to check the response. After that, all patients received Concurrent chemoradiation therapy (CCRT). CCRT includes administration of weekly Carboplatin AUC (area under curve) -2 with radiotherapy 5 days per week. Response was assessed according to the revised Response Evaluation Criteria in Solid Tumors (RECIST) criteria9 shown in Table-I.

Table-1: Definition of Response Assessment

Response Assessment	RECIST Guideline, Version 1.0
Evaluation of target lesions	
CR	Disappearance of all target lesions
PR	≥ 30% decrease in the sum of the longest diameters of target lesions compared with baseline
PD	≥ 20% increase in the sum of the longest diameter of target lesions compared with the smallest sum longest diameter recorded or the appearance of one or more new lesions
SD	Neither PR or PD

*CR=Complete response, PR= Partial response, PD= Progressive disease and SD= Stable disease

** RECIST: Response Evaluation Criteria in Solid Tumors*

Statistical Package for the Social Sciences (SPSS) version 23.00. was used to analyze the data. Mean and SD were reported for numeric variables. Frequency and percentage were reported for categorical data. Independent variables were compared with response using Chi-square/Fisher exact test. A *p*-value≤0.05 was taken as statistically significant.

RESULTS

A total of 71 patients with inoperable locally advanced head and neck squamous cell carcinoma were enrolled in the study. The mean age of study sample was 48.46±12.74 years (Range: 24-72 years). Around 54(76%) of the patients were males and 17(24%) were females. Of 71 patients, 45(63.4%) patients were urban residents, 49(69%) were outdoor workers and 28(39.4%) were Urdu speaking. Nine patients had hypertension (12.7%) and 12(16.9%) had a positive family history regarding head and neck cancers. Oral cavity was the most frequent site of tumor 38(53.5%). Approximately 51(72% of the patients had stage IV-A disease and 49(69%) had grade 2 (Table-II).

Most patients had partial response (PR),[9,10] after induction chemotherapy 45(63.4%). However, 12(16.9%) patients showed stable disease (SD), 10(14.1%) showed progressive disease (PD), and only 4(5.6%) showed complete response (CR)[7] (Figure-1).

Table-II: Baseline Characteristics of Study Participants (n=71)

Demographic Variables		Tumor-Related Variables	n (%)
Age in years (Mean±SD)	48.46±12.74	Family history	
	n (%)	Yes	12 (16.9)
Gender		No	59 (83.1)
Male	54 (76.1)	Site of Tumor	
Female	17 (23.9)	Oral cavity	38 (53.5)
Residence		Oropharynx	5 (7)
Urban	45 (63.4)	Hypopharynx	9 (12.7)
Rural	26 (36.6)	Nasopharynx	6 (8.5)
Occupation		Larynx	13 (18.3)
Indoor	22 (31)	Stage	
Outdoor	49 (69)	III	9 (12.7)
Ethnicity		IVA	51 (71.8)
Sindhi	21 (29.6)	IVB	11 (15.5)
Urdu	28 (39.4)	Grade	
Punjabi	4 (5.6)	Gx	2 (2.8)
Pashto	8 (11.3)	G1	14 (19.7)
Baloch	6 (8.5)	G2	49 (69)
Others	4 (5.6)	G3	6 (8.5)
Comorbidities			
Diabetes	2 (2.8)		
Hepatitis B	1 (1.4)		
Hypertension	9 (12.7)		

Table-III: Association of Concurrent Chemo Radiotherapy with Independent Variables (n=71)

	Response to Concurrent Chemoradiotherapy				*p*-value
	Complete Response	Partial Response	Stable Disease	Progressive Disease	
Age groups					
<45 years	9(37.5%)	8(30.8%)	4(40%)	6(54.5%)	0.599
≥45 years	15(62.5%)	18(69.2%)	6(60%)	5(45.5%)	
Gender					
Male	14(58.3%)	20(76.9%)	9(90%)	11(100%)	0.032*
Female	10(41.7%)	6(23.1%)	1(10%)	0	
Site of tumor					
Oral cavity	15(62.5%)	12(46.2%)	4(40%)	7(63.6%)	0.733
Oropharynx	2(8.3%)	2(7.7%)	1(10%)	0	
Hypopharynx	2(8.3%)	4(15.4%)	1(10%)	2(18.2%)	
Nasopharynx	3(12.5%)	3(11.5%)	0	0	
Larynx	2(8.3%)	5(19.2%)	4(40%)	2(18.2%)	
Stage of tumor					
III	4(16.7%)	2(7.7%)	3(30%)	0	0.31
IVA	17(70.8%)	21(80.8%)	5(50%)	8(72.7%)	
IVB	3(12.5%)	3(11.5%)	2(20%)	3(27.3%)	
Grade					
Gx	0	2(7.7%)	0	0	0.515
G1	6(25%)	5(19.2%)	3(30%)	0	
G2	15(62.5%)	17(65.4%)	7(70%)	10(90.9%)	
G3	3(12.5%)	2(7.7%)	0	1(9.1%)	
Response to Induction Chemotherapy					
Complete response	4(16.7%)	0	0	0	
Partial response	19(79.2%)	18(69.2%)	8(80%)	0	0.001*
Stable disease	0	8(30.8%)	2(20%)	2(18.2%)	
Progressive disease	1(4.2%)	0	0	9(81.8%)	

Out of 71 patients, 26(36.6%) achieved PR after CCRT, 24(33.8%) had achieved CR, 10(14.1%) had SD and 11(15.5%) had PD (Figure-2).

The proportion of PR to CR after CCRT was significantly higher among males than females (p=0.032). Nineteen patients who achieved PR after

Induction Chemotherapy (ICT) achieved CR after CCRT (79.2%), while the 4 who had CR after ICT, had maintained CR after CCRT (16.7%). On subset analysis ICT responders showed higher response rate to CCRT. There was statistically significant difference in response to ICT and response to CCRT (p=0.001, Table-III).

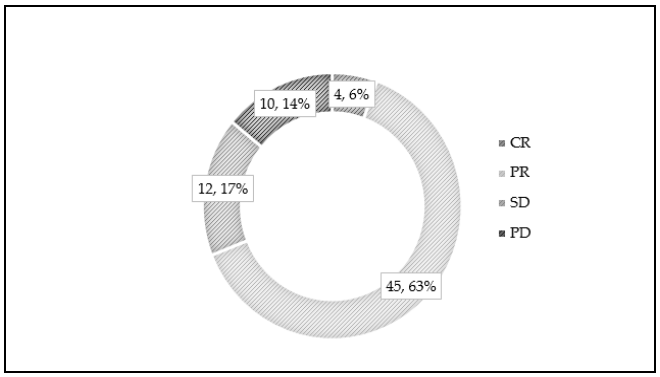

Figure-1: Response to Induction Chemotherapy in Locally Advanced Head and Neck Squamous Cell Carcinoma Patients (n=71)

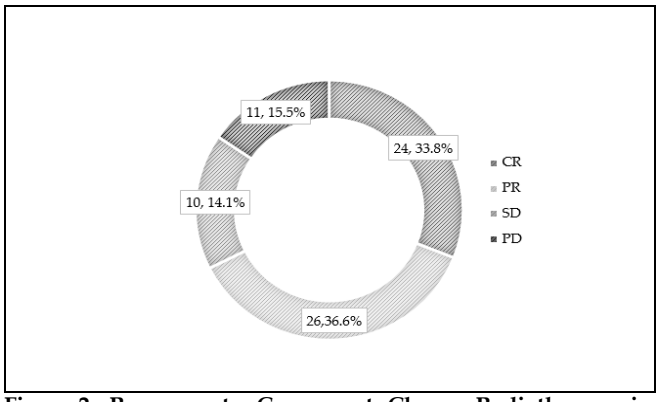

Figure-2: Response to Concurrent Chemo Radiotherapy in Locally Advanced Head and Neck Squamous Cell Carcinoma Patients (n=71)

DISCUSSION

Despite numerous studies, the role of induction chemotherapy remains under investigation. Ample data has been accumulated about the superiority and advantages of TPF (Cisplatin, Docetaxel, and Fluorouracil) over Cisplatin and Fluorouracil (PF) doublet chemotherapy.[11] In terms of longer intracellular half-life, Docetaxel has the advantage, resulting in a higher cellular level in the steady state.[12] In addition, with respect to bcl-2 inactivation and phosphorylation, Docetaxel is 100 times more active than paclitaxel, and can also act to stabilize tubulin.[12,13] Taxane has demonstrated a significant response as induction agent in combination with Cisplatin and Fluorouracil as well as in recurrent diseases.[12,13] Thus, in the current study we have evaluated the effect of ICT with TPF as a predictor of response to definitive CCRT in inoperable locally advanced squamous cell carcinoma of head and neck.

Literature shows that for LAHNSCC, induction with chemotherapy is a viable option before CCRT for the preservation of organs in larynx, hypopharynx and oropharynx.[14-16] Recently, protocols integrating sequential addition of ICT to CCRT tend to have an effect on reducing the occurrence of distant metastases.[17-19] In addition, different protocols have used ICT as a method of chemoselection to classify patients who will probably respond to CCRT. Even several randomized trials have used ICT response in their decision-making to provide successful responders with CCRT, whereas poor responders are given upfront surgery.[14]

In the study by Mizumachi *et al*., three cycles of ICT were given followed by CCRT and complete response was achieved in 86% of patients with LAHNSCC.[20] In another similar study by Paccagnella et al. complete response was achieved by 50%, whereas in the study by Prestwich et al. complete response to induction TPF followed by CCRT was achieved by 86% of LAHNSCC.[10,21] Ghi *et al*.,[5] also concluded that ICT followed by CCRT improved overall survival of patients with LAHNSCC. In the present study, patients with LAHNSCC were given three cycles of ICT (Docetaxel, Cisplatin and 5-FU-TPF). Sixty-three percent showed partial response and 6% showed complete response after three cycles. Patients were given CCRT after three cycles of ICT. Over 79% achieved complete response after ICT followed by CCRT. In a meta-analysis of 7 studies including 423 patients showed that pooled sensitivity and specificity of ICT response in prediction of CCRT response were 95% and 43% respectively.[14] Wang *et al*., in their trial evaluated the impact of induction TPF followed by CCRT in Asian patients and showed complete response in 14% of the patients after ICT and 60% partial response. Additionally, 42% achieved complete response following resection or radiotherapy.[22] Hence, these findings show that ICT responders also show good response to CCRT. Based on all previous studies and our study it is now evident that ICT is an ideal predictor of future response to definitive CCRT in locally advanced medically inoperable or technically unresectable HNSCC. On

one side these findings will help select patients who can really benefit from CCRT from those who are unlikely to benefit from this aggressive treatment modality. On the other hand, decreasing the unnecessary long waiting time for radiotherapy in potentially curative group of patients by omitting from the list, the non-responders of ICT.

CONCLUSION

Our study revealed that induction chemotherapy can predict response to concurrent chemoradiotherapy which can better inform patients and their families regarding disease outcome with CCRT. It can also help in selection of patients' future goal of treatment i.e. palliative vs. curative.

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Authors Contributions:

Following authors have made substantial contributions to the manuscript as under:

BAM & GH: Data acquisition, critical review, approval of the final version to be published.

TA & MA: Conception, study design, drafting the manuscript, approval of the final version to be published.

MA & SS: Data analysis, data interpretation, critical review, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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