Original Article

Response to induction chemotherapy as predictive marker of tumor response to radiotherapy and survival in oral cavity cancer

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ABSTRACT

Background: Trials have shown some statistically nonsignificant survival advantage of taxane, platin and 5-FU (TPF) induction chemotherapy before definitive chemoradiation. We tried to find the role of induction chemotherapy in the prediction of tumor response to radiotherapy and survival in the treatment of oral cavity cancers. **Patients and Methods:** Patients of stage III and IV (M0) unresectable oral cavity squamous cell carcinoma were assigned to receive two cycles of TPF. On the basis of response to chemotherapy, two groups were made. Those who had partial or more than partial response and another group who had stable disease or disease progression during chemotherapy. Concurrent chemoradiotherapy was given to all patients after induction chemotherapy. **Results:** A total of 128 patients who received TPF, 29 (22.6%) had complete response, 57 (44.5%) had partial response, 38 (29.7%) had stable disease and 4 (3.1%) had progressive disease. Definitive chemoradiotherapy lead to complete response in 48 (55.8%) patients who had partial or more than partial response (total 86) to chemotherapy and 10 (23.8%) patients among those who had stable disease or disease progression during chemotherapy (total 42). This difference in response is statistically significant ($P = 0.001$). Three years survival was significantly better after treatment in patients who responded more than partial (hazard ratio 0.463, 95% confidence interval 0.2789–0.7689), with an estimated 3-year survival of 35% in patients in group 1 and 14% in group 2. **Conclusion:** Response to induction chemotherapy can be a predictive marker for response to subsequent chemoradiotherapy and survival, with acceptable toxicities.

Key words: Chemoradiotherapy, induction chemotherapy, oral cavity cancer, predictive marker

INTRODUCTION

Head and neck malignancy constitutes 5% of all cancers worldwide and is sixth most common malignancy.[1] It is the most common malignancy in Indian male comprising 23% of all cancers.[2] Head and neck cancer also comprises 6% of all cancers in female. The disproportionately higher prevalence of head and neck cancer in relation to other malignancies in India may be due to the use of tobacco in various forms, consumption of alcohol and low socioeconomic conditions related to poor hygiene, poor diet or infection of viral origin. Oral cavity is the most common site of malignancy in head and neck region, comprising 55% of total head and neck cancers in India.[2]

Surgery followed by chemoradiation is standard of treatment in locally advanced disease with 5 years relative survival of 23.2% and 22.3% in oral cavity cancer (SEER data). Approximately, 50–60% of patients have local disease recurrence within 2 years, and 20–30% of patients develop metastatic disease.[3,4] Also, a substantial proportion of patients endure who were operated upon have significant functional aesthetic consequences.

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Organ preservation therapy is in vogue due to better results of newer chemotherapeutic regimen and addition of chemotherapy to curative treatment improves clinical outcomes in patients with advanced disease, demonstrating significant benefits in terms of organ preservation, longer time to disease progression, better locoregional control, fewer distant metastases, and longer overall survival time.[5] We studied if chemotherapy response can be a predictive marker for response of further chemoradiotherapy treatment and survival.

PATIENTS AND METHODS

Locally advanced inoperable cases of oral cavity cancers were selected from patients registered in J. K. Cancer Institute. Patients who gave written consent were enrolled for the study. Treatment naïve, histopathology proven locally advanced squamous cell carcinoma of oral cavity (stage III and stage IVA and IVB) cases with age <70 years and Eastern Cooperative Oncology Group performance status ≤1 were included in study. Patients with any co-morbid illnesses, where radiotherapy and/or chemotherapy becomes contraindication were not included in this study. Patients also had to have normal organ functions as defined by an absolute neutrophil count ≥1500 cells/μL, platelet count ≥100,000 cells/μL, total bilirubin <1.25 × the laboratory upper limit of normal, and a calculated creatinine clearance of more than 50 mL/min.

All patients received two cycles of induction chemotherapy every 3 weeks. Docetaxel 75 mg/m^2 was given intravenously on d1, cisplatin 75 mg/m^2 was administered intravenously on d1 and 5-FU 750 mg/m^2 d1–4 days by continuous intravenous infusion. Antiemetic protocol was aprepitant 125 mg PO taken 60 min before chemotherapy on day 1 and 80 mg PO on days 2–3; dexamethasone 12 mg PO and ondansetron 32 mg IV given 30 min before chemotherapy. Total leukocyte count and platelets count were done on alternate days from day 3 to day 15 of 1st day of chemotherapy of each cycle.

All the patients after receiving 2 cycles of chemotherapy were divided in two groups based on response of induction chemotherapy and both groups received same definitive treatment of concurrent chemoradiation within 3–4 weeks of start of second chemotherapy [Figure 1]. Chemotherapy was cisplatin 100 mg/m^2 on day 1, 22, and 43 of initiation of radiation. Total radiation to primary disease and involved node given was 66-70 Gy, two Gy per fraction, 5 days in a week by three-dimensional conformal radiotherapy. Uninvolved nodes received 50–60 Gy according to risk of microscopic disease.

Response evaluation was done after 15 days of completion of 2nd cycle of chemotherapy and 4 weeks after completion of chemoradiotherapy. Evaluation was according to Response Evaluation Criteria In Solid Tumors.

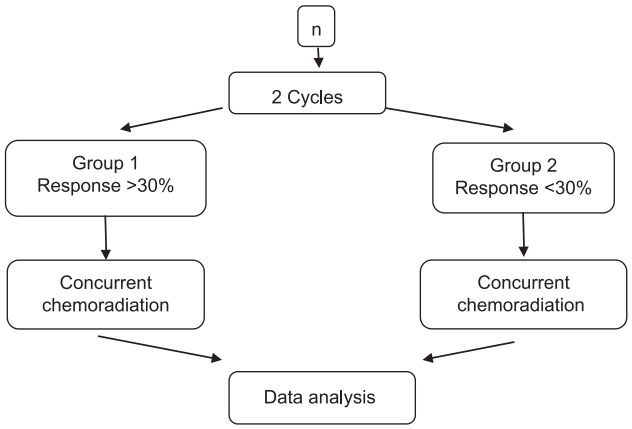

Figure 1: Study design

Patients with residual or recurrent disease were offered salvage chemotherapy or possible surgical intervention or palliative treatment.

Statistical analysis

Chi-square test was used to compare the response in two groups divided after induction chemotherapy. $P < 0.05$ was taken as significant and <0.01 as highly significant. Survival analysis was done using Kaplan–Meier survival curve and difference was shown by log-rank test.

RESULTS

Disease characteristics

Only squamous cell carcinoma was taken in this study. 76% of the cases were of grade I, 19% of grade II and 05% were in grade III. Nodal involvement with the early disease was common with tongue and its consistency with its high vascular supply. With the increase in size of tumor, probability of nodal involvement increased [Table 1]. The disease site, its vascular and lymphatic drainage are some confounding variables, which are disturbing the correlation.

Response to chemotherapy

Out of 128 of total cases, 29 (22.6%) had complete response, 57 (44.5%) had partial response, 38 (30%) had stable disease and 04 (03%) had progressive disease even after chemotherapy. Out of 50 patients in stage III, 40 (80%) had more than partial response with chemotherapy while out of 78 of stage IV patients, only 46 (59%) had more than partial response. This difference is statistically significant ($P = 0.013$) and signifies prognostic relevance of stage.

Induction chemotherapy toxicity

Major encountered toxicities were gastrointestinal and hematological but of grades I and II. Leukopenia of

grades III and IV was encountered in only 6 (4.6%) cases. Worrisome anemia and thrombocytopenia developed in 10.9% and 2.3% of study population respectively. Anemia developed in 11% of cases. Nephrotoxicity and oto-toxicity were not observed in the study population and neurotoxicity was complained by 1.6% of patients. Asthenia developed in almost all cases, but of the mild grade. Only 3.9% complained of grade III/IV asthenia. None of the patients developed febrile neutropenia [Table 2].

Based on response to chemotherapy, two groups were made. Mean and median age, standard deviation and standard error were calculated on two groups made on the basis of response to induction chemotherapy. There was no statistical difference in age of the two groups. Buccal mucosa and tongue being the most common site, but no statistically significant difference in distribution of patients of these sites in two groups ($P = 0.705$).

Definitive chemoradiotherapy lead to complete response in 48 (55.8%) patients who had partial or more than partial response (total 86) to chemotherapy and only 10 (23.8%) patients among those who had stable disease or disease progression during chemotherapy (total 42). This difference in response was statistically significant ($P = 0.001$). This magnitude of response ultimately translated to survival benefit on 3 years follow-up. Three years survival was significantly better after treatment in patients who responded more than partial (hazard ratio 0.463, 95% confidence interval 0.2789–0.7689), with an estimated 3-year survival of 38% in patients in group 1 and 13% in group 2 [Figure 2].

Mucositis, radiation dermatitis, xerostomia, laryngeal edema and dysphagia were most common radiation-related grades III and IV reactions in both groups, but there was no statistical significant difference in incidences [Table 3]. None of the patients interrupted treatment due to radiation reactions and were managed conservatively.

Table 1: Nodal distribution according to tumor size

Site	T_1	T_2	T_3	T_4
BM	-	N_1-4 N_2-4	N_0-6 N_1-8 N_2-4 N_3-2	N_0-14 N_1-11 N_2-7 N_3-4
Tongue	N_3-2	N_1-12	N_1-3 N_2-3	N_0-2 N_1-12 N_2-10
RMT	-	N_1-2	N_0-2 N_1-2	-
Gingiva	-	N_1-4 N_2-2	N_0-2	N_0-2 N_2-6
FOM	-	-	-	N_1-2 N_2-2

BM: Buccal mucosa, RMT: Retromolar trigone, FOM: Floor of mouth

Table 2: Side effects of TPF chemotherapy

Side effect (grades III and IV)	Incidence (%)
Leukopenia	6 (4.6)
Anemia	14 (10.9)
Thrombocytopenia	3 (2.3)
Nausea	2 (1.6)
Vomiting	3 (2.3)
Diarrhoea	5 (3.9)
Asthenia	5 (3.9)
Alopecia	13 (10.1)
Oral mucositis	7 (5.5)
Neurotoxicity	2 (1.6)
Oto-toxicity	0

DISCUSSION

This study demonstrates definitive improvement in complete response in those patients who responded well with induction chemotherapy. This initial complete response rate signifies survival benefit. Patients in group 1 had a reduction of 54% in the risk of death, an improvement in the median of 3 years survival of 13 months, and an absolute increase in 3-year survival of 25%.

Taxane, platin and 5-FU (TPF) regimen was selected based on phase II/III trials showing benefit in response and survival than cisplatin and 5-FU combination in similar unresectable stage, but also in resectable III and IV head neck cancer population.[6-13] Meta-analysis by Pignon *et al*. which included 31 induction studies, all but two suggested no survival benefit[14]. In the meta-analysis, studies from 1965 to 1993 were included, though in updated analysis studies from 1994 to 2000 were also included, but in that era taxane use was not frequent.[13]

Neoadjuvant chemotherapy trials, TAX 323 and 324 both published results in 2007. TAX 324 trial, included patients both with resectable disease and those with unresectable disease, however in TAX 323 only unresectable disease

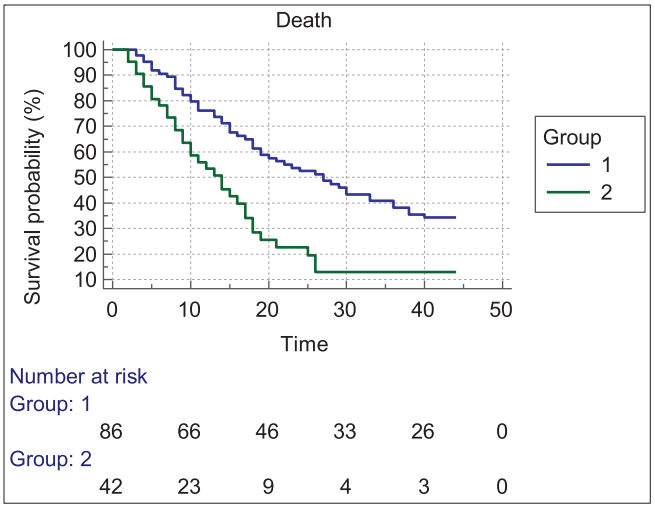

Figure 2: Three years survival Estimated by Kaplan meier survival method Group 1 denotes patients with more than partial response with induction chemotherapy and group 2 denotes patients with less than partial response.

population was included as in our study. Two more phase II studies by Paccagnella *et al*. and Hitt *et al*. also included unresectable head neck disease and reported the benefit of adding neoadjuvant TPF chemotherapy before radiotherapy. Hitt trial showed survival benefit only in patients with the unresectable disease (median survival, 36 months in the PPF group and 26 months in the PF group).

The response rate in TAX 323 was 68% while in our study it is 67%, almost equal response rate. Comparative analysis of four major neoadjuvant chemotherapy trials is shown in Table 4. Other parameters are not comparable in these studies because of a different line of treatment and study design.

Major toxicities with chemotherapy regime were as expected and manageable and hardly lead to treatment interruption. Gastrointestinal and hematological toxicities were predominant toxicities. Chemoradiotherapy regimen was also well tolerated. In conclusion, Induction chemotherapy can be a predictive marker for response to further treatment of chemoradiation and survival, with acceptable toxicities.

Table 3: Patients characteristics and treatment responses

	Group A	Group B	Total	*P*
	86	42	128	
Age (year)				
Mean	46.28	45	45.86	0.705
Median	46	42	45	
Range	22-67	25-70	22-70	
Age *n* (%)				
20-30	7 (8.13)	3 (7.14)	10 (7.81)	
30-40	18 (20.93)	10 (23.80)	28 (21.87)	
40-50	34 (39.53)	15 (35.71)	49 (38.28)	
50-60	12 (13.95)	4 (9.52)	16 (12.50)	
60-70	15 (17.44)	10 (23.80)	25 (19.53)	
Site *n* (%)				
BM	35 (40.69)	23 (54.76)	58 (45.31)	0.189
Tongue	31 (36.04)	13 (30.95)	44 (34.37)	0.71
RMT	4 (4.65)	2 (4.76)	6 (4.68)	
Gingiva	14 (16.27)	2 (4.76)	16 (12.50)	
FOM	2 (2.32)	2 (4.76)	4 (3.12)	
Result				
CR	48	10	58	0.001
Residual	38	32	70	
3 years survival				
Live	30	05	35	0.011
Dead	56	37	93	
Reactions *n*	Grade III/IV	Grade III/IV		NS
Mucositis	25	14		0.773
Radiation dermatitis	03	02		0.892
Laryngeal edema	10	9		0.231
Dysphagia	12	12		0.080
Xerostomia	17	13		0.238

BM: Buccal mucosa, RMT: Retromolar trigone, FOM: Floor of mouth, NS: Nonsignificant, CR: Complete response

Table 4: Response comparison in different trials

	This study	TAX 323	TAX 324	Hitt *et al.*	Paccagnella *et al.*
CR	22.6	8.5	17	33	6.5
PR	44.5	59.3	55	47	63
Overall response	67.1	67.8	72	80	69.5

CR: Complete response, PR: Partial response

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Conflict of interest

There are no conflict of interest.

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