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Oncology

NEOADJUVANT CHEMOTHERAPY IN LOCALLY ADVANCED INOPERABLE CARCINOMA BUCCAL MUCOSA -A CASE SERIES.

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ABSTRACT

Background: Carcinoma buccal is the most common subsite in carcinoma oral cavity owing to increased use of oral tobacco among Indians. Majority of the patients present with locally advanced disease and are inoperable. The role of neoadjuvant chemotherapy are being explored with the premise of downstaging and improving operability, thereby increasing progression free survival and overall survival.

Aim: To evaluate the impact of neoadjuvant chemotherapy in locally advanced, unresectable carcinoma buccal mucosa.

Materials and Methods: Single institutional retrospective analysis of patients with locally advanced carcinoma buccal mucosa, who were treated with neoadjuvant chemotherapy (NACT) during the period 2017 and 2018. Data regarding patient characteristics, chemotherapy received, response rates, local treatment offered, disease free survival and overall survival analysed.

Result: A total of 27 patients received chemotherapy. Median age been 40 years. 20 of our patients received three drug regimen while the rest of our patients received two drug regimen. Among them 14 underwent curative surgery. Pathologic complete response in 6 patients and pathologic partial response achieved in 4 patients. Median Progression free survival and overall survival for patients neoadjuvant chemotherapy are 9 months and 14 months respectively. Median PFS and OS for patients with pathologic complete response on surgery were 14 and 20 months respectively.

Conclusion: Induction chemotherapy was able to downsize tumour, associated with marginally improved progression free survival and overall survival in comparison to nonsurgical treatment.

KEYWORDS :

INTRODUCTION:

Oral cavity cancer comprises majority of cancers in India [1-3]. Incidence of carcinoma buccal mucosa is high compared to other oral cavity subsites [4]. Around 60% cases of buccal cancers present with advanced stage and patients tend to have multiple risk factors [5-6]. Surgery is preferred treatment of choice for resectable disease and unresectable disease are treated with concurrent chemoradiation [7]. Literatures have shown subset of patients with T4b carcinoma buccal mucosa can be treated with surgery if clear margins are possible [8]. Experience with induction chemotherapy in a selected population of technically unresectable tumours have shown favourable outcomes in some centres [9]. Neoadjuvant chemotherapy (NACT) in buccal mucosa cancer can cause tumour shrinkage, which could improve locoregional control (LRC) and overall survival (OS) and may help to achieve organ preservation in resectable oral cavity cancers. NACT may also be used in patients with borderline resectable/ technically unresectable tumours to reduce the surgical margins, increase resectability, and achieve R0 resection and in unresectable tumour to improve disease-free survival (DFS) and OS [10]. This case series reviews experience with NACT in locally advanced in carcinoma buccal mucosa in a tertiary centre in chennai between year 2017 -2018.

METHODS:

Retrospective review was conducted of all patients who received neoadjuvant chemotherapy for locally advanced and unresectable carcinoma buccal mucosa in a dedicated cancer centre in a tertiary care hospital in south India between years 2017 -2018. The data was retrieved from the medical records, case files and hospital cancer registry. A total of 77 carcinoma buccal mucosa patients were treated in our cancer centre during 2017 and 2018. Among them 46 patients had stage IVA &IVB. 27 patients had neoadjuvant chemotherapy 2 patients defaulted during treatment and 4 patients lost follow up. The management of all patients were decided in the multidisciplinary tumour board at our centre. Locally advanced Buccal mucosa primary, with diffuse margins, peritumoral oedema going up to or above the level of zygomatic arch and without any satellite nodules, involvement of infratemporal fossa, extensive skin infiltration impacting the achievement of negative margins were inoperable and selected for NACT. Patients with frank skull base invasion, prevertebral fascia involvement, carotid encasement were considered inoperable and were excluded. The chemotherapy regimens had 2 or 3 drugs consist of combination of a taxane (paclitaxel or docetaxel) and a platinum (cisplatin) with 5-fluorouracil. The choice of regimens was decided on the patient's performance status, creatinine clearance as calculated by the Cockcroft–Gault formula[11-14]. After two cycles of chemotherapy, response was assessed clinically and radiologically according to the RECIST 1.1 criteria. The patients, whose tumours had sufficiently regressed assessed by the operating surgeon, were considered resectable. These patients underwent surgery followed by adjuvant therapy. The surgical resections planned were according to the post chemotherapy volume. The remaining patients underwent radical chemoradiation, radical radiation, palliative chemotherapy, or best supportive care according to their performance status, disease status and informed choice. Patient demographic characteristics (e.g., age), treatment offered, pathology, and outcomes were collected, tabulated, and correlated with outcomes. IBM SPSS statistics software for windows, version 21.0 (Armonk, NY: IBM Corp) was used for data analysis.

RESULTS:

Clinicopathological Factors(TABLE 1):

Between January of 2017 and January of 2018, 27 patients were retrospectively analysed. Median age was 40 years. Male (85.2%) were more common than female (14.8%). Patients had comorbities such as diabetes 25.9%, systemic hypertension 25.9%, coronary artery disease 18.5%. Mean of basic blood parameters were haemoglobin - 13.07±2.05gm/dl, albumin - 3.6±0.45 mg/dl, creatinine – 0.90± 0.14 mg/dl. All patients had performance status of ECOG 1. Frequency of habits were, 60.8 % among male and 75% among female had oral tobacco use, smoking was present in 69.5% among males. There were no smokers and alcohol use among females. Alcohol intake was present in 34.7% among male. Synchronous smoking and alcohol were present in 22.2%. Two patients did not have any habits.

Tumour staging details (TABLE 1).

All patients had TNM stage IV disease based on AJCC staging system 7th edition. The tumour T stage was cT4a in 20 patients (74%), cT4b in 7 patients (25.9%). N staging, cN0 in 1 patient (3.7%), cN1 in 13 patients (48.1%), cN2a in 8 patient (29.6%), cN2b in 3 patients (11.1%), cN2c in 2 patients (7.4%). All patients were squamous cell carcinoma (SCC)with 74.1% well differentiated SCC and 25.9% moderately differentiated SCC.

Chemotherapy details (TABLE 2):

Three drug regimen was administered in 20 patient (74%). Among three drugs 11 patients (40.7%) received docetaxel along with cisplatin and 5FU, 9 patients (33.3%) received paclitaxel along with cisplatin and 5FU. Among two drug regimen 7 patients (25.9%) received only cisplatin and 5FU.

Among 20 who had 3 drug regimen 14 patients (70%) underwent curative surgery. No patients from 2 drug regimen had surgery. 13 patients (48.1%) underwent chemoradiation following neoadjuvant chemotherapy.

Response to chemotherapy (FIGURE 2).
Overall response rate (ORR) post treatment is 51.8%, with 8 complete response and 6 partial response in patients. Among 10 patients who had surgery 6 patients (60%) had pathological complete response and 4 patients (40%) had partial response to neoadjuvant chemotherapy.

Recurrence and survival (FIGURE 2-4).
Totally 6 patients had recurrence among 8 CR on follow up . One Patient developed synchronous malignancy during treatment. Median Progression free survival and overall survival 9 months and 14 months, respectively. Median progression free survival in pathologic complete response and partial response are 14 months and 8 months. Median overall survival in pathological complete response and partial response are 20 months and 11 months.

DISCUSSION

Oral cancer is the sixth most common type of cancer with India contributing to almost one-third of the total burden. Tobacco consumption including smokeless tobacco, betel-quid chewing, excessive alcohol consumption, unhygienic oral condition, and sustained viral infections that include the human papillomavirus are some of the risk aspects for the incidence of oral cancer [15]. The management of carcinoma buccal mucosa has been surgical resection as the mainstay of treatment, and outcomes have remained stable over the past two decades with 5-year overall survival (OS) of approximately 60% for all comers and 33–54% for patients with locally-advanced disease [16-17]. Studies for preoperative therapy for oral cavity squamous cell carcinoma began by 1989 and patients were given cisplatin and infusion 5FU and study included stage II, III and IV. A pathologic complete response of the primary tumour was 27%, and persistence of microscopic residual disease at the T site was 18% [18]. Phase 3 trials using different combination of neoadjuvant chemotherapy in resectable oral cavity squamous cell carcinoma failed to show improved locoregional control and overall survival when compared to surgery followed by adjuvant chemoradiation [19]. Few Phase 3 trails have shown improved resectability, progression free survival and overall survival for neoadjuvant chemotherapy followed by surgery in unresectable locally advanced oral cavity squamous cell carcinoma. Patil et al. analysed patients with technically unresectable OSCC, all of whom received two or three drugs (taxane + platinum ± 5FU) as NACT followed by resection in resectable cases. Nearly 43% of the patients had downsizing of disease and subsequently underwent surgery with R0 resection. The LRC rate at 2 years was 20.6% for the whole cohort. The median OS was 19.6 months for patients who underwent surgery [19-20]. We retrospectively analysed only locally advanced unresectable carcinoma buccal mucosa since it has poor response to chemoradiation compared to other subsites of oral cavity. 27 cases of unresectable carcinoma buccal mucosa was treated with neoadjuvant chemotherapy in our centre during year 2017 and 2018 and 21 patients were under follow up. Unresectability was based on diffuse margins, peritumoral oedema going up to or above the level of zygomatic arch, involvement of infratemporal fossa, extensive skin infiltration impacting the achievement of negative margins. Patients received either three or two drug chemotherapy regimens. Three drugs consisted of taxanes in addition to cisplatin and 5FU. Two drug regimens consisted of cisplatin and 5FU alone. Most of the patient had habits of oral or smoking tobacco. All were in ECOG 1 and had adequate renal function.

In patient treated with NACT three drug regimen (74%) either docetaxel or paclitaxel were used depending on comorbid status of patient. Most of the patient in 3 drug regimens had downstaging of tumour and underwent surgery.

All surgery had R0 resection and 6 patients (60%) had pathological complete response. Median progression free survival was 9 months and Overall survival was 14 months. Overall survival in patient who had complete pathological response was 20 months. The OS advantage demonstrated in our analysis from use neoadjuvant treatment and surgery are encouraging. However, chemotherapy was given only to carefully selected patient with good performance status and avoided in overt comorbid status. Further prospective randomization with large number of patients is necessary to show survival benefits.

CONCLUSION:

The use of induction chemotherapy in locally advanced unresectable carcinoma buccal mucosa is feasible, can cause tumour downstaging thereby making them operable. This approach is likely to lead to a survival advantage in patients. More multi-institutional trials in larger cohorts with prospectively collected data are required to arrive at a definite conclusion or protocol with NACT that may make a difference in unresectable oral malignancies.

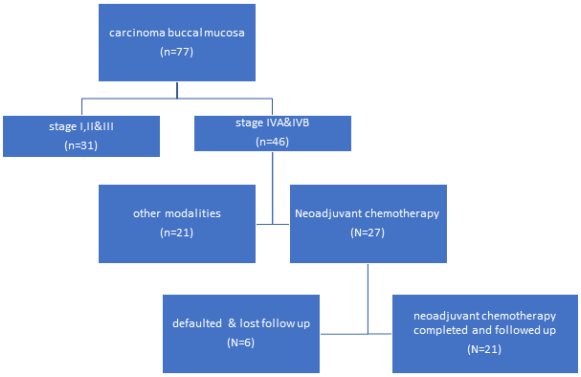

Figure 1 : Consort Flow Diagram

Table 1

MEDIAN AGE	40
MALE/FEMALE	23/4
T STAGE	
T4a	20
T4b	7
N STAGE	
N0	1
N1	13
N2a	8
N2b	3
N2c	2
REASON FOR CHEMOTHERAPY	
EXTENSIVE SKIN INVOLVENT	15
PTYREGOID PLATES INVOLEMENT	5
EXTENSIVE PERITUMORAL EDEMA	5

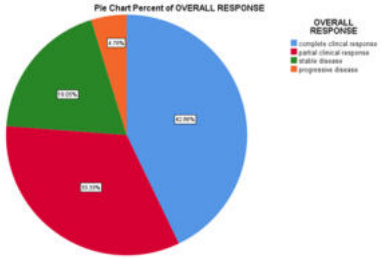

Figure 2 : Overall Response

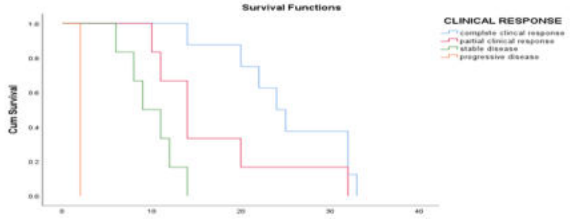

Figure 3: Kaplan-meier Curve Showing Os In Realtion To Response.

OS in months

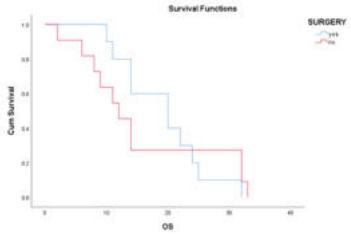

Figure 4: Kaplan-merier Curve Showing Os In Relation To Surgery

Table 2

CHEMOTHERAPY	
DOCETAXEL+ CISPLATIN+5FU	11
PACLITAXEL+CISPLATIN+5FU	9
CISPLATIN+5FU	7
SURGERY	
3 DRUG	14
2 DRUG	0
PATHOLOGICAL RESPONSE TO CHEMOTHERAPY	
DOCETAXEL+CISPLATIN+5FU	
COMPLETE RESPONSE	3
PARTIAL RESPONSE	3
PACLITAXEL+CISPLATIN+5FU	
COMPLETE RESPONSE	3
PARTIAL RESPONSE	1

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