



THE EFFECT OF NEOADJUVANT CHEMOTHERAPY ON LOCAL CONTROL AND SURVIVAL IN HEAD NECK CANCER PATIENTS IN A TERTIARY CARE HOSPITAL IN INDIA: A RETROSPECTIVE ANALYSIS

Oncology

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ABSTRACT

Context: Head and neck squamous cell carcinoma (HNSCC) is the sixth most common cancer worldwide. Mostly, patients present in the locally advanced stage. Induction chemotherapy has been repeatedly associated with tumour shrinkage and decreased risk of distant metastases. Unfortunately, improvement in overall survival with induction chemotherapy, over standard treatment approaches, has not been definitively demonstrated.

Aims: 1. To determine the local control rates with induction chemotherapy regimens
2. To evaluate the effect on Disease Free Survival with induction chemotherapy upto a period of two years
3. To determine the frequency and severity of toxicities with induction chemotherapy

Settings and Design: Single institution retrospective observational study in a tertiary care hospital.

Methods and Material: 50 patients of HNSCC, who had first attended the outpatient department in 2014 and had received neoadjuvant chemotherapy (NACT), were selected. Patient characteristics, indications and details of NACT, mode of treatment received and final outcome were noted from case record files of the patients.

Statistical analysis used: IBM SPSS version 23.

Results: Male preponderance. Commonest occurrence in the sixth decade. Commonest subsite - pyriform sinus. 24% patients were referred for surgery but only 4% actually underwent surgery. In 84% cases, taxane-based regimens used. Commonest indication for NACT - to bridge the long waiting time for definitive treatment. 8% grade three toxicities noted, commonest being vomiting. After a median follow up of 1.5 years, 52% patients were disease free. 14% patients had recurrence, maximum in the pyriform sinus.

Conclusions: Patients responding well to NACT were mostly disease free after treatment completion, had survival benefit. Taxane-based regimen showed survival advantage, good disease control with organ preservation.

KEYWORDS

neoadjuvant chemotherapy, taxane-based regimen, bridge long waiting time

INTRODUCTION:

Head and neck squamous cell carcinoma (HNSCC) is the sixth most common cancer worldwide [1]. In India, cancer of the lip and oral cavity is the most common cancer among males with 119,992 new cases diagnosed and 72,616 deaths in 2018 so far [2].

The several risk factors for developing HNSCC include genetic background, geographical location, diet, tobacco and alcohol abuse. Cigarette smoking and excessive alcohol consumption, besides being independent risk factors, also have a synergistic effect [3,4]. Apart from these, reverse smoking, that is, the habit of keeping the lighted end of the cigarette in mouth while smoking and chewing of betel quid (paan) consisting of betel leaves, areca nut and slaked lime, are also widespread in India, predisposing the patients to HNSCC. Recently, association of high risk types of Human Papilloma Virus (HPV), particularly HPV-16 has also been implicated in the development of HNSCC [5].

Majority of the HNSCC occur in patients above 50 years of age, with the average age of diagnosis for smoking related HNSCC being 60 years [6]. The stage at diagnosis is the most important determinant of prognosis - the 5-year survival rate for Stage I patients being more than 80%, but in locally advanced head and neck carcinoma (LAHNC), it is less than 40% [7]. In India, most of the patients present in the locally advanced stage. LAHNC are usually treated with combination therapy including surgery, radiotherapy and chemotherapy [7,8]. Neoadjuvant chemotherapy (NACT) in HNSCC has been studied for more than three decades, being repeatedly associated with tumour shrinkage and decreased risk of distant metastases [9,10]. The meta-analysis of chemotherapy on head and neck cancer, of 63 trials involving more than 10,000 patients failed to demonstrate significant survival benefit following induction chemotherapy [11]. However, the trials that used 5-fluorouracil (5-FU) and cisplatin as a part of NACT regimen showed significant overall survival (OS) benefit compared to other combination regimens and single agent NACT [11,12]. Most of these trials were from the pretaxane era, and impact of taxanes in the

neoadjuvant setting is not addressed in with this meta-analysis. The interest in NACT has been rekindled by recent studies such as TAX 323 and TAX 324 which included taxane (docetaxel) along with 5-fluorouracil and cisplatin containing (TPF) regimen. The TPF induction regimen showed improved survival in advanced HNSCC as compared to patients receiving an induction regimen with cisplatin and fluorouracil (PF) alone [13,14,15]. To assess the effects of specific induction chemotherapy regimens as well as the treatment approach itself, compared with no induction chemotherapy, a meta-analysis of randomized trials was conducted by Hitt R. et al - comparison of survival outcomes revealed that the risk for death was lower with the use of PF induction chemotherapy, compared with no induction chemotherapy, docetaxel-based regimen was associated with a lower risk for death than PF and similar findings were made on the risk for disease progression [16].

Our aim was to evaluate the local control rates, survival benefit and to determine the toxicities associated with induction chemotherapy prior to definitive treatment in HNSCC and thereby exploring the usefulness of NACT in reducing surgical margins, decreasing the risk of distant metastasis and improving outcomes in HNSCC.

METHODS:

A retrospective, observational, single institutional study carried out in a tertiary care institute.

Prior approval was obtained from the Institutional Ethics Committee before starting the study.

Patients with newly diagnosed histologically proved HNSCC, between stages I to IVB, who had first attended the Oncology OPD in 2014 and received neoadjuvant chemotherapy, were selected as subjects. The case record files of these subjects were used to collect the following data –

Age group
Gender

Site of disease
 Histology
 Clinical stage
 Indications for neoadjuvant chemotherapy
 Dose and Regimens used
 Number of cycles administered
 Side effects experienced during and after neoadjuvant chemotherapy
 Response to neoadjuvant chemotherapy
 Mode of treatment received
 Final outcome.
 Follow up data till the year 2017 was obtained, median duration of follow up being 1.5 years. The data collected was then analyzed using IBM SPSS software (version 23).

RESULTS:

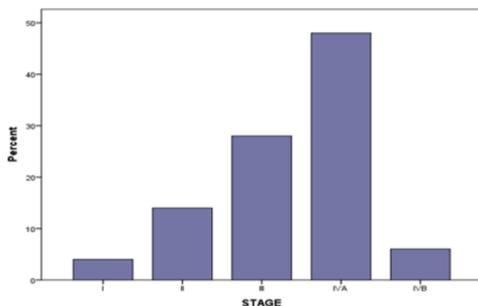
The patient characteristics noted were as follows –

GENDER	FREQUENCY	PERCENT
MALE	45	90
FEMALE	5	10
TOTAL	50	100

SITE	FREQUENCY	PERCENT
Retromolar Trigone	5	10
Glottic Larynx	2	4
Maxilla	1	2
Base of Tongue	8	16
Nasopharynx	3	6
Buccal Mucosa	6	12
Pyriform Sinus	15	30
Anterior 2/3rd Tongue	2	4
Soft Palate	1	2
Supraglottic Larynx	7	14
TOTAL	50	100

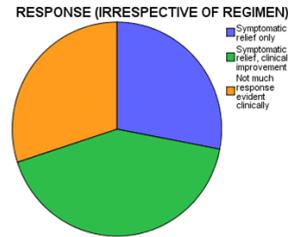
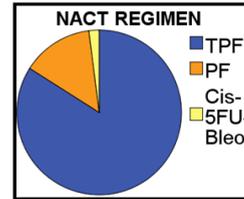
AGE	FREQUENCY	PERCENT
< 30 yrs	2	4
30 - 40 yrs	5	10
41 – 50 yrs	13	26
51 – 60 yrs	11	22
61 – 70 yrs	15	30
71 – 80 yrs	4	8
TOTAL	50	100

HISTOLOGY	FREQUENCY	PERCENT
Well differentiated	16	32
Moderately differentiated	26	52
Poorly differentiated	8	16
TOTAL	50	100



Among the various indications noted for neoadjuvant chemotherapy, commonest was to bridge the long waiting time for definitive treatment (90%). Most of the patients had multiple indications for induction chemotherapy.

NACT INDICATION	FREQUENCY	PERCENT
Bridge long waiting time for Surgery	12	24
Symptomatic Relief	38	76
Downstaging	26	52
Bridge long waiting time for Radiotherapy	34	68
Growth Restraining	24	48
Survival Advantage	13	26



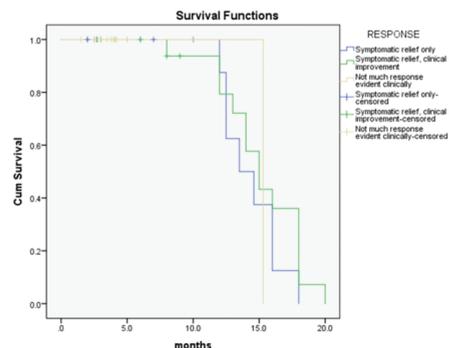
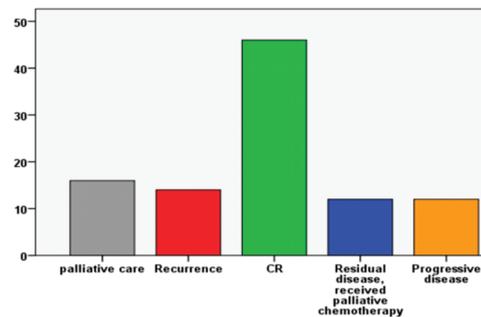
NACT regimens were administered as shown in the figure.

The frequency of side effects to induction chemotherapy were as follows – nausea (50%) > fatigue (48%) > vomiting (22%) > dysgeusia (16%) > mucositis (10%) > neutropenia (2%). Only 8% patients had Grade 3 toxicity, commonest being vomiting.

24% patients were referred for surgery but only 4% of the total 50 patients actually underwent surgery. Majority of the patients (66%) received radical radiotherapy (66 Gy in 33 fractions) as the definitive treatment. Out of the 4% patients who underwent radical surgery, half of them received post-operative radiotherapy.

Using multiple linear regression, the effect of NACT regimen and the number of cycles used, on response, was determined. In our analysis, taxane-based neoadjuvant chemotherapy showed survival advantage, good disease control and helped in organ preservation in technically unresectable HNSCC. More number of cycles resulted in better response. However, none of the results were statistically significant (P > .05).

The final outcomes are represented in the figure below –



After a median follow up of 1.5 years, 46% patients were disease free, with pattern of disease freeness as follows – nasopharynx (100%) > supraglottic larynx (57.1%) > pyriform sinus (53.3%) > buccal mucosa (50%), glottis larynx (50%), anterior 2/3rd of tongue (50%) > base of tongue (37.5%). 14% patients had recurrence, the subsite with maximum recurrence being pyriform sinus.

It was observed that those who had responded well to induction chemotherapy mostly had survival benefit over others after completion of treatment and were mostly disease free after treatment completion.

DISCUSSION:

The main aims of this study were to evaluate the local control rates, overall survival and to determine the toxicities associated with induction chemotherapy prior to definitive treatment in HNSCC. Majority of the HNSCC patients in India present in the locally advanced stage when it is difficult to deliver upfront radical treatment. Induction chemotherapy, which has been found to be associated with tumour shrinkage and possibly decreased risk of distant metastasis, has long been studied with no conclusive evidence on survival benefit over standard treatment approaches. In our study, male preponderance was observed among HNSCC patients (M:F = 9:1) with commonest occurrence in the sixth decade of life. Majority of the patients presented in stage IVA, with moderately differentiated squamous cell carcinoma, the commonest site being pyriform sinus. The most common indication for neoadjuvant chemotherapy noted was to bridge the long waiting time for definitive treatment although, in most cases, there were multiple indications. Most patients received taxane-based regimen (docetaxel-cisplatin-5Fluorouracil) and they showed better response compared to the other regimens in terms of local disease control, organ preservation, survival advantage. In our study, after a median follow up of 1.5 years, only 42% were disease free. Patients with nasopharyngeal carcinomas were found to be benefitted most (100%). Carcinomas of the pyriform sinus showed most aggressive behaviour, with maximum recurrence. 30% patients had poor response to induction chemotherapy. Major side effects of induction chemotherapy were found to be loss of appetite and fatigue which were tolerated by most patients. Only 8% patients experienced grade 3 toxicity, vomiting being the most common. It was also observed that good responders to induction chemotherapy were mostly disease free after treatment completion and had survival advantage over others. However, our study has several limitations – small sample size, short duration of follow up, being a retrospective observational study. Hence, the results need to be validated by more prospective studies, with large sample size and longer duration of follow up in future.

Acknowledgement:

We are extremely grateful to Dr. Bodhisattwa Dutta, Dr. Rumeli Roy, Dr. Debashis Das, Dr. Nibediata Biswas, Dr. Snigdha Hazra and Dr. Anish Dasgupta – Department of Radiation Oncology, Medical College and Hospital, Kolkata for their constant support.

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