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Induction Chemotherapy in Unresectable or Locally Advanced Head and Neck Squamous Cell Cancer: A Single Center Retrospective Experience

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Abstract

Head and Neck Squamous Cell Carcinoma (HNSCC), have an unsatisfactory prognosis despite intensive local treatment. Single institution retrospective study of 60 patients, who were treated with induction chemotherapy followed by Concurrent chemo radiation for period between January 2012 to December 2012 to understand utility of Induction Chemotherapy (IC), response rates and outcome analysis of patients with locally advanced and non-metastatic HNSCC. 38 out of 60 patients (63.3%) received all 3 planned IC cycles and 15 (25%) patients completed only 2 out of 3 cycles and rest of patients defaulted during course of chemotherapy. Only 32 patients had clinical benefit (CBR 38%), 12 patients had CR (20%), 11 patients had PR (18%), and SD in 9 patients (15%) on IC therapy. 20 (33.33%) patients received subsequent radiation treatment following IC. Among 20 patients who received subsequent radiation treatment, 17 were treated with radical intent and 3 with palliative intent. Remaining 40 (66.67%) failed to receive any further treatment. At last only 12 out of 17 patients received concurrent chemo radiotherapy following Induction chemotherapy and five disease free survival rate was 46%. Induction chemotherapy is almost always associated with poor patient compliance to planned definitive treatment in developing country. Innovative and individualized approach for patient compliance is required. Periodic assessment of induction chemotherapy response, target therapies and early initiation of radiation therapy in non-responder should be the cornerstone of future strategy.

Keywords: Concurrent Chemoradiation; Induction Chemotherapy; Locally Advanced Head and Neck Squamous Cell Cancer; Treatment Outcomes; Response Rate.

Introduction

Head and Neck Squamous Cell Carcinoma (HNSCC) is sixth commonest malignancy in world with approximately 6,00,000 patients being diagnosed annually.[1]In India alone, there are about 77,000 cases detected every year and are significant problem in our country constitute approximately one-third of all cancer cases in contrast to 4–5% in the developed world [2,3]. About 60%-70% patients, will present with advanced locoregional disease which are accounting for significant morbidity and mortality [4,5]. Historically, patients with locoregionally advanced head and neck cancer who are treated with local therapy will develop locoregional recurrence in 50 to 60% and distant metastasis in another 20% to 30% of all cases. For unresectable head and neck cancer, the 5-year survival rate with RT alone is less than 25% [6]. Chemoradiotherapy gained a wider acceptance with the publication of the pivotal MACH-NC [7]. This meta-analysis of 10,741 patients with resectable and unresectable cancer of the oropharynx, oral cavity, larynx, and hypopharynx, had compared induction, concurrent, and adjuvant chemotherapy to locoregional therapy alone. The study revealed that chemotherapy delivered either by neoadjuvant or concurrent or adjuvant carried an absolute survival benefit of 4% at 5 years ($p < .0001$). Concurrent chemotherapy was found to produce the greatest benefit, with an absolute overall survival benefit of 8% at 5 years (27% vs. 35%, $p < .0001$). Thus, the concomitant chemoradiation

therapy (CRT) has become the acceptable option care in the management of most locally advanced head and neck cancer [8,9,10]. In contrast, induction chemotherapy was found to have a statistically insignificant overall survival benefit of 2% at 5 years despite using either suboptimal IC or inadequate concurrent regimens. However, a 5 yr OS of 5% was observed when analyses were restricted to trials using an IC regimen composed of cisplatin and fluorouracil [5,11]. When more intensive CRT was used, there was improvement in 3-year local control rate with lesser distant metastasis [12].

Limited Randomised Control Trails (RCTs) exists which comparing the standard treatment of CRT versus IC followed by CRT so the role of IC is not yet clear. Two individual trials have shown a survival benefit for IC followed by local treatment (surgery + RT / RT alone) over local treatment alone [13,14,15]. More recently, phase III studies from the EORTC/TAX study group comparing two IC regimens consisting of cisplatin and fluorouracil with or without Docetaxel followed by CRT in patients with unresectable Squamous cell carcinoma of the head and neck found a significant improvement in the progression free and overall survival with inclusion of docetaxel [16,17]. Now IC is beneficial for reducing the rate of distant metastasis, increasing organ preservation and survival rates and also used when radiation therapy could not be started within a reasonable timeframe [13,14,17]. IC is also preferred for patients with N3 disease, in whom shrinkage of the tumour was desirable to diminish radiation fields and limit toxicities. To understand the utility of IC, this single center retrospective outcome analysis of patients with locally advanced, non-metastatic HNSCC who were treated with IC followed by CRT was conducted.

Materials & Methods

Objectives

To assess the outcomes in terms of treatment completion rate, Response rate, 5-year disease free survival and treatment compliance in unresectable and radiation ineligible locally advanced non-metastatic HNSCC patients who underwent IC followed by CRT. Estimation of 5-year survival rate in patients who completed planned treatment and on follow up care was done.

Patients

The data of demographic details, age, sex, socioeconomic status, education, KPS, subsite of head & neck, stage, intent, treatment planned were recorded. (Table 1). Criteria for unresectability of the primary site or adenopathy include fixation to the spine or prevertebral muscles or involvement of skin, dura, base of skull, or brachial plexus. Some patients are also categorized as unresectable due to the expectation of poor functional outcomes following surgery. Also, patients may be considered unresectable due to significant medical co morbidities, rendering them unable to tolerate the extensive resections required for locally advanced disease. Also, when radiotherapy could not be started within a reasonable time frame due to extensive disease or reoccurrence after local surgery or significant co-morbidities were considered for study. These Patients who were initially planned for induction chemotherapy followed by concurrent chemo radiotherapy (CRT) (n =60) were included for the present study irrespective of the final treatment received by them. Further data required for analysis are collected by reviewing medical records of chemotherapy and radiation charts for data collection and follow up details.

Study design

Retrospectively analysis of case records of patients with unresectable locally advanced, non-metastatic HNSCC patients treated from 1st January 2012 to 31st Dec 2012 at M.S. Ramaiah hospitals, with IC followed by CRT. Inclusion criteria were: 1) Stage III or IVA-B unresectable Squamous cell carcinoma according to the 7th edition of American Joint Committee on Cancer staging criteria and patient's criteria defined earlier; 2) Patients who had received IC and CRT following IC. Study was approved by institute ethical committee

Treatment

Reports of the 60 patients with unresectable locally advanced HNSCC i.e. with T4/N3 disease, who met the inclusion criteria, were taken up for this study and all details regarding chemotherapy regimen and drug doses were noted. Numbers of cycles completed were recorded and response evaluation was done using RECIST (Response evaluation criteria in solid tumors) guidelines. Choice of chemotherapy regimen and dose was decided by medical oncologist based on age, KPS, nutritional status of patient and tumor factors. Patients who were planned with doublet chemotherapy were scheduled to receive total 3 cycles with 3 weekly

regimens and with triplet chemotherapy for total 3 cycles with 3 weekly regimens. Two cycles were scheduled only for patients with specific co-morbidities and/or with an age of more than 65 years. For IC or concurrent chemotherapy, dose reductions were applied for patients receiving cisplatin for renal and haematological toxicities. Radiotherapy (RT) details were collected from RT charts of patients retrospectively, to note the intent of treatment. The radiation therapy dose was 66 Gy to the primary tumour and nodes involved as per post induction chemotherapy CT scan. The adjacent nodal regions at risk received were 50 to 60 Gy. Treatment was delivered with a 6 MV linear accelerator in standard fractionation using 3D CRT / IMRT technique.

Follow-up

Patients were clinically examined during their follow up period which was every 2 weekly for the first 2 months then once in 4 -6 months up to 5 yrs or till 31/12/2017. Every patient had a computed tomography (CT) scan six to eight weeks after definitive treatment or when the physical exam was suspicious of recurrence. A chest radiograph was also performed periodically. The cross-sectional follow up data at 5 yr after treatment completion was collected.

Statistical analysis

Performance status of patients was measured using the Karnofsky performance status scale [18]. Clinical adverse events and drug toxicity were measured using National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE; version 3.0) [19]. Radiologic studies were done, and tumor response was evaluated using Response Evaluation Criteria in Solid Tumors 1.0 criteria. Radiologic and clinical response was determined in terms of complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD) [20]. Overall response rate (ORR) was defined as the combination of CR, and PR. Clinical benefit rate (CBR) was defined as the combination of CR, PR, and SD. Five year Disease-free-survival (5 yrs. DFS) was defined as the time interval between initiation of chemotherapy and documentation of progression or censored at the time of death or the final follow-up done after 5 years of starting chemotherapy. Direct survival analysis was used to calculate 5 yrs-DFS for selected patient who have completed IC and are on follow up.

Results

Patient characteristics

Sixty patients were planned to receive IC followed by CRT for unresectable locally advanced SCCHN. Table 1 summarizes the demographics and clinical characteristics of these patients. The mean age at diagnosis was 54.18 years, with men composing 73.33% of the patient population. Most patients had oropharyngeal cancer (46.67%). Majority were in stage IVA, about 60%.

Table 1: Patient Characteristics.

	#Patients (percent)
Total number of patients	60
Age	
Mean	54 yrs.
Sex	
male	44(73.33)
female	16(26.67)
KPS	
Mean	76.27
Primary tumour sites	
Nasopharynx	3(5)
Oral cavity	5(8.33)
Oropharynx	28(46.67)
Larynx	15(25)
Hypopharynx	7(11.67)
Nodal only disease with Unknown primary	2(3.33)
Stage	
III	19(31.67)
IVA	36(60)
IVB	5(8.3)

Treatment characteristics

Treatment characteristics are listed in Table 2. Patients were treated with combination of 5 FU with either platinum or methotrexate-based regimens. Most of the patients (71%) received platinum-based IC regimen. Cisplatin was preferred over carboplatin as concurrent chemo radiation regime. Median dose was 66 Gy radiation was delivered either 3D CRT/ IMRT techniques. Following Induction chemotherapy (IC), only 38 (63.3%) out of 60 patients received all 3 cycles planned and 15 (25%) patients completed only 2 out of 3 cycles and rest of patients defaulted during course of chemotherapy. Among 32 patients who received IC and had clinical benefit (CBR 38%), 12 patients had CR (20%), 11 patients had PR (18%), and SD in 9 patients (15%). (Table 3) Response assessment was not possible in 22 patients (36%) who were lost to follow up either due to toxicities or non-compliance despite good initial response. Overall, 20 out of 60 patients only 1/3rd (n= 20) patients were found to have receiving subsequent radiation treatment. Among 20 patients who received subsequent radiation treatment, 17 were treated with radical intent and 3 with palliative intent. (Table 4) Overall only 12 out of 17 patients received concurrent chemo radiotherapy as per initial plan. Five disease free survival rate was in this group was 46%. Remaining 40 (66.67%) patients who received only IC without radiation due to unacceptable toxicities, disease progression, treatment noncompliance and follow up defaulter, were excluded from analysis.

Table 2: Treatment Characteristics

	#Patients (percent)
Induction Chemotherapy	
Carbo-5FU	3(5)
Cisplatin-5FU	24(40)
Docetaxel+cisplatin5+ Fluorouracil	16(26.67)
Methotrexate -5FU	17(28.33)
Number of cycles	
1 cycle	7(11.67)
2 cycles	15 (25)
3 cycles	38 (63.33)

Table 3: Outcomes of Induction Chemotherapy(IC).

Response Parameters	**No of patients**	**%**
Complete response	12	20.00
Partial response	11	18.33
No response/Stable disease	9	15.00
Progressive disease	6	10.00
Response could not be assessed		
Defaulted during course of IC	15	25.00
Metastasis during course of IC	1	1.67
Mortality during course of IC	6	10.00
Total	60	100.00

Table 4: sequence of patient's treatment after Induction chemotherapy

Treatment	**No of patients**	**% of patients out of 60**
IC -->CTRT	12	20.00
IC--> RT	5	8.33
IC --> RT PALLIATIVE	3	5.00
Total	20	33.33

Discussion

Head and neck Squamous cell carcinomas (HNSCC) have an unsatisfactory prognosis on IC primed local treatment despite strong rationale of Induction chemotherapy being beneficial for reducing the rate of distant metastasis, increasing organ preservation and survival rates. Several advantages of Induction chemotherapy include the delivery of doses of chemotherapy to untreated, well vascularised tumours as well as the eradication of micro metastatic disease. Moreover, induction chemotherapy reduces tumour burden before local treatment. In addition, a patient might better tolerate a chemotherapy treatment if not administered with radiation therapy. Previously reported studies have shown comparable two years rates for OS (61-66%), LRC (71-76%) and DMFS (79-91%) [21,22]. However, these studies had larger inclusion criteria such as inclusion of nasopharynx, inclusion of T1N2 or T3N1 patients whereas our study only had one patient with stage III, IVA, IVB disease. Several phase II studies confirmed that IC achieved objective tumour regression in 60-90% of the patients with a clinical complete response in 20-50% can be compared to our study with 20% patients showing complete response [23,24]. Phase II studies have shown the benefit of combining Docetaxel to cisplatin and fluorouracil [24,25]. Posner and al. also conducted a randomised phase III study (TAX 324 Study Group) demonstrating that patients who received Docetaxel plus cisplatin and fluorouracil IC followed by CRT had a significantly longer survival than did patients who received cisplatin and fluorouracil IC followed by CRT [26]. However, the concomitant regimen used weekly carboplatin, a therapy that is not standard and unproven by a phase III trial and could be potentially suboptimal therefore underestimating the results associated with the arm without Docetaxel in the IC regimen. In many published trials, head and neck tumours are treated by CRT with 2-3 cycles of high dose cisplatin [10, 27, and 28]. In fact, many ongoing trials use cisplatin as the standard arm in randomized trials of head and neck cancer where concurrent chemo radiation is part of the definitive treatment. Moreover, Brizel and Vokes suggested that the benefit of taxanes may diminish as the intensity of local-regional therapy increases [29]. In the present study, most patients received only 2 cycles of IC. This did not cause much delay in the administration of the treatment of choice for advanced SCCHN, CRT. In a phase II study by Urba et al. a single cycle of IC was given to stage III-IV Squamous cell carcinoma of the larynx. Patients with less than 50% response underwent total laryngectomy and the remainder underwent CRT [30]. They obtained a 70% rate of larynx preservation. They believe, and our results concur with the premise that speed of tumour response to neoadjuvant chemotherapy is an important prognostic factor. Reducing overall treatment time to diminish accelerated repopulation of surviving clonogens is an important radiobiology concept. Further research with biological markers might answer the question as to why patients with the same baseline characteristics respond differently to treatment. There might be predictive biomarkers that would help in choosing between an IC option or not. Where shrinkage of the tumour is necessary for radiotherapy fields to be safe are offered IC. In such, we believe that if IC must be given, it should be restrained to only one or two cycles.

The limitations of our study include its retrospective single site accrual with relative small sample, inadvertent bias in selecting IC regimes and suboptimal toxicities data capture despite standard radiation techniques and supportive care.

Conclusions

Induction chemotherapy is almost always associated with poor compliance of patient to planned final treatment in developing country. Innovative and individualized approach for patient compliance is required. Periodic assessment of induction chemotherapy response and early initiation of radiation therapy in non-responder should be the cornerstone of future strategy. In this single-centre retrospective analysis, despite intensive treatment with platinum-based IC and CRT, prognosis for this highly advanced population of stage III & IV cancers is poor. Our cohort of patients resulted heterogeneous results in term of treatment completion, response rates, and outcomes when compared to previous studies. Novel targeted agents, such as EGFR antagonists might yield more promising results when used in the regimen of IC. Research is warranted for prognostic variants and biomarkers which could help in selecting patients who might benefit from IC.

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Conflict of Interest - Nil

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