A Comparative Study between Patients Receiving Induction Chemotherapy and Conventional Weekly Cisplatin in Locally Advanced Head and Neck Cancer Undergoing Radiation

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ABSTRACT

BACKGROUND

As most cases of head and neck cancer are locally advanced, i.e., stage III and IV, it may be useful to compare induction chemotherapy policies accompanied by simultaneous chemoradiation with concomitant chemoradiation alone, in terms of tumour response and toxicity profile in these cases. That's why this study was undertaken. We wanted to evaluate induction chemotherapy accompanied by chemoradiation in terms of local regulation as opposed to chemoradiation alone in locally advanced Head and Neck Cancers.

METHODS

This is a prospective comparative study. Study was done between July 2017 and July 2019, with Arm A (Test Group) & Arm B (Control group). Forty patients of locally advanced Head and Neck cancer from the outpatient department, selected for treatment, were included in the study, with 20 in each arm.

RESULTS

Reduction in tumour size after treatment was compared in both the groups with RECIST (Response Evaluation Criteria in Solid Tumours) 1.1. Induction chemotherapy caused significant reduction in tumour size but had more toxicities which were manageable. When compared to conventional chemoradiation, the induction chemo group did not show statistically significant benefit. Response was better in patients with high nodal volume as some of the cases showed good response in the nodal volume irrespective of response of the primary.

CONCLUSIONS

This study emphasizes the role of induction chemotherapy in select patients with advanced disease, especially in high volume, where majority of cases (more than 80 %) are stage III or IV and above. Hence, patient selection is the key to outweigh the risk involved.

KEYWORDS

Cancer Undergoing Radiation Therapy

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BACKGROUND

Head and neck cancer is the 6th most common in the world, accounting for more than 550,000 new cases and 380,000 deaths annually.[1] South East Asia is expected to see dramatic rises in the number of deaths from cancer by more than 75 per cent in 2020 compared to 2000. More than 2 lakh cases of head and neck are diagnosed annually in India.[2] In India, 60 to 80 percent of advanced-illness patients are present compared to 40 percent in developed countries. Since the percentage increase in the Indian population has been nearly twice that of the world in the last fifteen years, there is a possibility that the cancer burden will rise with the same proportion. The real burden of head and neck cancer in India is far greater than reflected in current literature and can therefore be regarded as an 'iceberg top' situation. The distribution of registries of population-based cancer is highly unequal with some important sections of the country not being identified at all and hence the actual cancer burden is not reflected in the registry results.[3]

Statistics from the MNJ Regional Cancer Center, Hyderabad, show that over the past 5 years about 2857 new cases of head and neck cancer have been reported, among a total of 22468 cancer cases, representing about 12.7 percent of the total new cancer cases. Some are stage III and stage IV cancers. The standard treatment scheme for cancers of the head and neck has included radiotherapy, surgery, and chemotherapy. The main objective is to achieve control of the loco-regions. Following standard therapy for advanced carcinoma of the head and neck, the 5-year survival rate is less than 50 %.[4,5] Therefore, new treatment protocols are being studied in order to achieve better survival and toxicity associated with lesser treatment. Traditional standard treatment suggests the use of surgery followed by adjuvant chemo-radiotherapy or upfront radical radiotherapy along with simultaneous chemotherapy. That said, chemotherapy has also been explored as an upfront treatment (neo-adjuvant / induction) for locally advanced head and neck cancers. The main objective of this type of treatment is to reduce the tumour burden which helps to give better margins for radiation therapy treatment. Induction chemotherapy also helps to control remote micro metastasis, several studies have shown a decrease in distant failure rates. Reports from single institutions indicated response rates ranging from 70 % to 90 % in patients treated with cisplatin-based regimens, with complete clinical responses ranging from 20 % to 50 %. Docetaxel, cisplatin, and 5-fluorouracil [TPF (Taxotere Platinol Fluorouracil)] have become accepted induction chemotherapy regimen in Head and Neck Squamous Cell Carcinoma (HNSCC). But the carboplatin–paclitaxel [CT (Carbo-Taxol)] regimens showed similar or better performance. Compared to chemotherapy caused by TPF, in patients with less renal toxicity, CT induction chemotherapy had at least comparable if not better Loco-Regional Control (LRC) and Progression Free Survival (PFS). Given that the majority of head and neck cases in this institute are locally advanced, i.e., stage III and IV, it may be useful to compare induction chemotherapy policies accompanied by concurrent chemoradiation with concurrent chemoradiation alone in these cases in terms of tumour response and toxicity profile. That is why this research was conducted.

METHODS

This is a prospective comparative study conducted among forty patients of locally advanced head and neck cancer undergoing treatment in the outpatient department between July 2017 and July 2019. Twenty patients were selected in each arm. Patients with newly biopsy proven larynx, hypopharynx and oropharynx squamous cell carcinomas staged III-IV being treated with neoadjuvant chemotherapy are considered as study population.

Arm A (Test Group) – Induction chemotherapy accompanied by concomitant chemoradiotherapy with paclitaxel and carboplatin.

Arm B (Control group) - Concurrent chemoradiotherapy only.

All the eligible subjects willing to participate in the study were sampled consecutively into the study, hence no sampling was done**.**

The baseline sum of the targets lesions using RECIST criteria shall be calculated before the treatment and at first follow up using Computed Tomography (CT). At first follow-up with RECIST criteria the target lesions will be evaluated and allocated either to Complete Response (CR), Partial Response (PR), Stable Disease (SD) or Progressive Disease (PD). The patients were also evaluated with CTCAE (Common Terminology Criteria for Adverse Events); version 4.0) (951) for toxicity of chemotherapy and radiotherapy per week. Three key parameters, that is, nausea, dysphagia, and mucositis, were evaluated.

Inclusion Criteria

Age- 20 - 60 Years**,** tumour classified as stage III to IV located in oropharynx, hypopharynx, larynx according to the TNM (Tumour Node Metastasis) classification [AJCC (American Joint Committee on Cancer) 8th edition]**,** histopathological analysis of primary-site invasive squamous cell carcinoma and ECOG (Eastern Cooperative Oncology Group) performance status patients 0 and 1.

Exclusion Criteria

Prior surgical excision, the existence of synchronous multiple malignancies, planned elective surgery, previous history of radiation to head and neck, distant metastases, non-squamous histologies.

History and physical examination including height, weight, Body Surface Area (BSA) and state of performance.

1. Histopathologic proof of squamous cell carcinoma.
2. Complete blood count with differential counts, platelets, blood urea, serum creatinine, random blood sugar and liver function tests, viral markers.
3. CT scan of head and neck for baseline target lesion measurement using RECIST criteria.
4. Ultrasonography of abdomen and pelvis.

5. Chest X-ray (PA view) as a routine workup.
6. Staging of the cancer using AJCC 8th edition.

Treatment

Neoadjuvant Chemotherapy (NACT) Administration

Twenty of the selected patients for the study group (Arm-A) will receive NACT for two cycles with paclitaxel 175 mg / metre square and carboplatin (area under curve-5 / 6). Each cycle is of 21 days. Paclitaxel is administered in a glass bottle of normal saline and a codon set which has an inline filter in order to avoid leeching of plastic material used in normal saline bottles and I.V. sets. Carboplatin dosage was calculated using Calvert equation: = Target area under the curve (AUC) x (GFR* + 25)

Radiation Therapy Delivery

Two weeks after receiving NACT for 2 cycles the patients received radical chemoradiation with external beam radiation using conventional 2D technique for 66 Gray in 33 fractions (#) at the rate of 2Gy / # with concurrent Weekly Cisplatin 40 mg / metre square for 5 or 6 cycles at the rate of 1 cycle per 5 fractions. The control arm (Arm-B) also received conventional chemoradiation with similar dose scheduling but without receiving prior NACT.

Process of Radiotherapy Delivery

Immobilization- Patients were immobilized in supine position. With hands by the side of body and pulled down as much as possible on a four clamp. Base plate with customized thermoplastic mask after placing patient on an appropriate neck rest.

Simulation

Patient is simulated in supine position on flat couch in the dedicated CT-simulator facility at MNJ Institute of Oncology and Research Centre. Simulation is done by using 16 slice Philips CT simulator, 3 mm CT axial cuts of the patient are acquired with immobilization devices and fiducials. Fiducials are used to mark virtual iso-centre and it was also useful to reproduce the simulated position while treating.

Planning

The CT images are exported to 3D – Eclipse 13.6 planning system in DICOM (Digital Imaging and Communications in Medicine) format. All of the cases were planned with parallel opposed right and left lateral fields and a direct anterior lower neck field. The field borders varied slightly depending on the subsite of the cancer.

Treatment Delivery

All patients were treated by Varian linear accelerator machine with Source to Axis Distance (SAD) 100 cm.

Follow-Up

Both arms (A and B) shall be assessed for local response by RECIST criteria (using CT scan) on first follow up at 2 months after completion of treatment. All the patients shall be assigned a category to either Complete response (CR) / Partial response (PR) / Stable disease (SD) or Progressive disease (PD) depending on the reduction or increase in the baseline sum (CT scan) taken prior to treatment.

Statistical Analysis

Statistical Package for Social Sciences (SPSS version 20.0) and Microsoft Office Excel were used statistical analysis.

RESULTS

All the patients were evaluated at baseline and at first follow up two months after treatment using CT scan and readings were noted. Toxicities have been compared in two arms based on the highest grade of dysphagia / mucositis and nausea recorded during treatment.

Variant	Number	Percentage
Test Group		
Well Differentiated	6	30
Moderately Differentiated	12	60
Poorly Differentiated	1	5
Sarcomatoid	1	5
Control Group		
Well Differentiated	5	30
Moderately Differentiated	13	60
Poorly Differentiated	2	5

Table 1. Frequency Distribution of Histology / Differentiation in Test Group

Site	No. in Test group	No. in Control group	Percent	Percent
Supraglottis	11	6	55	30
Pyriform Sinus	3	5	15	25
Post Cricoid	3	4	15	20
Posterior Pharyngeal Wall	1	2	5	10
Tonsil	0	1	0	5
Soft Palate	2	1	10	5
Base of Tongue	0	1	0	5

Table 2. Showing Primary Involved Sites in the Test and Control Groups

Grade	Frequency	Percent
Nausea Test		
1	1	5
2	4	20
3	15	75
Nausea Control		
1	2	10
2	12	60
3	6	30
Dysphagia Test		
2	5	25
3	13	65
4	2	10
Dysphagia Control		
1	3	15
2	9	45
3	6	30
4	2	10
Mucositis Test		
1	4	20
2	10	50
3	6	30
Mucositis Control		
0	2	10
1	12	60
2	6	30

Table 3. Overall Toxicities during the Treatment

In the test group, 25 % were females and 75 % were males and in the control group, 35 % were females and 65

% were males. Minimum age was 24 and maximum age was 60. 55 % in test group and 65 % in control group consumed smokeless tobacco. Smoking was calculated using pack years with an average of 9.8 pack years in test group and 11.3 pack years in control group. Only one person from test group and one from control group are non-alcoholics. 95 % in both the groups are alcohol consumers in some form or the other. All the cases in test and control group were squamous cell carcinomas with various differentiations.

Carcinoma of the larynx was the most common primary in both groups with supra-glottis being the only subsite**.**

Overall toxicities during the treatment were *more in the test grou*p with nausea grade 3 (75 % vs. 30 %). Dysphagia grade 3 and 4 (65 % and 10 % vs. 30 % and 10 %); mucositis grade 2 and above (50 % vs. 30 %) in the test group and control group respectively. ORR was 90 % in test group vs. 80 % in control group. By conventional criteria, this difference is considered to be not statistically significant.

	TEST Group	Control Group
Complete Response (CR)	55 %	35 %
Partial Response (PR)	35 %	45 %
Stable Disease (SD)	10 %	20 %
Progressive Disease (PD)	0 %	0 %
Overall Response Rate (ORR)	**90 %**	**80 %**

Table 4. Comparison of Responses in Both Groups

DISCUSSION

This study aims at evaluating the role of induction chemotherapy in locally advanced larynx, oropharynx, and hypopharynx cancers. As majority of the cases at our institute are locally advanced, induction chemotherapy might play a crucial role at least in selected cases if not all. Therefore, use of this approach might be ideal in these cases even though chemoradiotherapy or surgery have been the standard approaches since decades.

Most of the studies done on induction chemotherapy have used cisplatin and 5-fluorouracil or TPF (Taxane, platinum and 5-fluorouracil) as induction regimens. Paclitaxel and carboplatin regimen is a new combination already well-established in ovarian, lung, breast, oesophagus and other metastatic settings. Its role in induction in head and neck is being explored recently in order to reduce the toxicity caused by previously used drugs. Before starting treatment baseline sum of the longest diameters were noted using CT scans and RECIST criteria in both the arms. Two cycles of chemotherapy were given to test group followed by chemoradiation with weekly cisplatin, the total treatment lasted about 12 - 13 weeks. The control group that received only chemoradiation had a treatment time of 7 - 8 weeks on an average depending on multiple factors and logistics. Patients were clinically stable during the study and all toxicities were managed according to protocols. Majority of the population were males with 75 % in test group and 65 % in control group. Overall males were 28 and females were 12 in both the groups. Age group wise 51 to 60 years old were most common in both the groups with 10 (50 %) in both control and test groups. Minimum age was 24 and maximum age was 60, median age was 52, this suggests that majority of head and neck cancers are elderly according to different cancer registries all over the world. All the cases in test and control group were squamous cell carcinomas with various differentiations. Moderately differentiated squamous cell carcinoma was the most common variant (60 and 65 %) followed by well differentiated type (30 and 25 %) and poorly differentiated type in (5 and 10 %) in test and control group respectively. Sarcomatoid variant of squamous cell carcinoma was seen in a single case of test group, it usually carries a poor prognosis compared to other variants. Carcinoma of the larynx was the most common in both groups with supra-glottis being the only subsite in both the groups. Supra-glottis carcinoma was 55 % and 30 %, pyriform fossa was the second most common site with 15 % and 25 %, post cricoid 15 % and 20 %, posterior pharyngeal wall 5 % and 10 %, tonsil 0 % and 5 %, Soft palate 10 % and 5 %, base of the tongue 0 % and 5 % in test and control group respectively.

Toxicities

Three parameters were assessed in both the groups which are nausea, dysphagia and mucositis. Overall toxicities during the treatment were moderately more in the test group with grade 3 nausea requiring intervention seen in 75 % in test group and 30 % in control group. Dysphagia grade 3 and 4 – 65 % and 10 % (test) vs. 30 % and 10 % (control). Mucositis grade 2 and above – 50 % vs. 30 % in the test group and control group respectively. Four patients (20 %) in test group required to stop radiation due to toxicities and two (10 %) persons in control group required radiation stoppage for 2 to 3 days. The baseline sum of the target lesions on CT scan was calculated for all patients on a diagnostic scanner. After the treatment in both the groups patients were called for first follow-up and another CT scan was done to measure increase or decrease in target lesion. Response assessment done on first follow-up with CT scans and RECIST criteria showed complete response that is, complete disappearance of target lesions for 55 % and 35 % in test and control group respectively. Partial Response in 35 % and 45 %, stable disease in 10 % and 20 % in test and control groups respectively. These results are similar if not better than the study done by Ajit Kuma et al.[6,7] None of the studied subjects had any progressive disease. For clinical purpose the lesions were categorized into primary lesions and nodal lesions. In general response of the nodal targets was better compared to response of the primary in both the groups. In test group primary responses were CR - 55 % PR - 35 % whereas nodal responses were CR - 75 % PR - 20 % clearly showing better nodal response. Similarly, in control group primary response was CR-35 % PR - 45 % and nodal response CR - 45 % PR - 40 %.

Overall response rate calculated as CR + PR were 90 % in test group and 80 % in control group. In the test group there was a total reduction of 127.1 centimetres in the baseline sum (baseline total 199.5 cm and first follow up sum 72.4 cm) with a mean of 6.355 centimetres (Std. Error of Mean .56603 and Std. Deviation 2.53138) with p value of 7.90628 X 10 - 10 (< 0.01) calculated using t-Test: Paired

two sample for means. In the control group there was a total reduction of 111.7 centimetres (baseline total 188.5 cm and first follow up sum 76.8 cm) in the baseline sum with a mean of 5.585 centimetres (Std. Error of Mean. 44160 and Std. Deviation 1.97492) with a p value of 1.06 X 10 - 10 (< 0.01) calculated using t-Test: Paired Two Sample for Means. Both the groups showed a statistically significant reduction in the baseline sum according to the calculated p value. To compare the results of the two groups which is the main aim of our study a paired T-test was performed between them for statistical analysis. At 95 % confidence intervals ranging from - 2.2034 to 0.7034 the p-value was 0.3028 which was insufficient to reject null hypothesis. Therefore, even though the response rates were better in the Test group compared to the control group, the data is statistically insignificant when compared between the groups. But the response was significant within the test and control groups with p value 7.90628 X 10 - 10 (< 0.01) and 1.06 X 10 - 10 (< 0.01) respectively.

In their study of 62 patients named paclitaxel induction and carboplatin for patients with carcinoma of the head and neck Frank R. Dunphy et al.[5] 74 per cent had stage IV disease, study concluded that paclitaxel induction and carboplatin tolerated well. The response rate was positive given the majority of patients were in stage IV. Several recent Phase III studies have assessed taxanes' function as ICs in head and neck cancer. The TAX 323 research contrasted the three-drug induction with TPF (docetaxel, cisplatin, and 5-FU) with the normal two-drug induction with PF for up to four cycles accompanied by RT in both arms in patients with unresectable head and neck cancer. The PFS with TPF induction was substantially longer (11 vs. 8.2 months; P = 0.007).[6] The TAX 324 analysis compared three periods of TPF vs. PF-IC followed by CRT in locally advanced resectable and unresectable head and neck cancer. Long-term follow-up found that the median OS was significantly longer in the TPF arm (71 vs. 35 months, P = 0.013). A recently published meta-analysis of five MACH-NC trials comparing induction Tax (paclitaxel or docetaxel) PF versus PF in LAHNC resulted in a death HR of 0.79 (95 percent CI: 0.70 – 0.89; P < 0.001) and an absolute 5-year gain of 7.4 percent in favour of Tax-PF.[8] Tax-PF was also correlated with major deterioration declines, locoregional failure, and distant failure co-incidence The authors concluded that although the induction of Tax-PF must be considered one of the criteria for the protection of larynx, further research in patients at high risk of metastasis is needed and its precise role in LAHNC management compared with the upfront CRT needs to be established.

Two recent trials have evaluated IC followed by CRT in head and neck cancer. The paradigm trial compared 3 cycles of TPF-IC followed by cisplatin-based CRT versus CRT. The trial was stopped early due to slow enrolment. The 3-year OS was similar, 73 % versus 78 % for IC versus CRT alone, respectively (p = 0.77).[9] The decide study compared CRT alone to two cycles of IC followed by CRT with docetaxel-based regimens in LAHNC.[10] Although OS was similar in both arms (HR: 0.91; 95 % CI: 0.59 – 1.41), the IC arm had a lower incidence of distant failure (p = 0.043). Like the PARADIGM study, the DECIDE study also did not meet its accrual target. As anticipated, both studies had higher incidence of toxicity, especially febrile neutropenia, in the IC arm.

Lauren C. Herman et al[11] performed a significant study comparing well-established TPF regimen to TP, study concluded that CT induction chemotherapy in patients had at least equal if not better LRC and PFS compared to TPF induction chemotherapy, and thus had less renal toxicity. CT induction chemotherapy can thus support patients with locally advanced HNSCC by promoting appropriate chemoradiation regimens to improve control of disease.

Study	Details	Results
Frank R. Dunphy et al 2009[5]	IC in head and neck cancers with Paclitaxel and Carboplatin	ORR- 66 % OS benefit for responding hypopharynx / oropharynx vs non responders (55 % vs. 27 %; P = 0.04)
TAX 324 study 2007	IC with TPF vs PF followed CRT	The median OS was significantly longer in the TPF arm (71 vs. 35 months, P = 0.013)
MACH-NC 2013[8]	IC with TPF vs PF	Absolute benefit of 7.4 % at 5 years in favour of Tax- PF
PARADIGM 2013[9]	3 cycles of TPF-IC followed by cisplatin-based CRT versus CRT	The 3-year OS was similar, 73 % versus 78 % for IC versus CRT alone, respectively (P = 0.77)
DECIDE 2014[10]	CRT alone to 2 cycles of IC followed by CRT with docetaxel-based regimens	Although OS was similar in both arms, the IC arm had a lower incidence of distant failure (P = 0.043)
Lauren C. Herman et al 2014[11]	TPF vs CT induction chemotherapy (IC)	The 1-year locoregional control was 80.5 percent for CT compared to 55.5 percent for TPF (HR 0.32, P = .0002) The study concluded that in patients with less renal toxicity, CT induction chemotherapy had at least comparable if not better LRC and PFS compared with TPF induction chemotherapy.
Ajit Kumar, Neha Kurmi[12] Patel, Lalit Mohan Patel 2019[12]	Carboplatin and Paclitaxel as Induction Chemotherapy – retrospective study	Of the 250 patients studied, 101 (40.4 %) showed partial response, 84 patients (33.6 %) showed complete response, 25 patients (10 %) persisted with stable disease and 40 patients showed progressive disease

Table 5. Comparison Table of the Relevant Studies

Most recent study conducted by Ajit Kumar et al[12] in India published in Feb 2019 called ''Carboplatin and Paclitaxel as Induction Chemotherapy in Locally Advanced Head and Neck Cancer Patients ''. This a retrospective study of the 250 patients studied, 101 (40.4 %) showed partial response, 84 patients (33.6 %) showed complete response, 25 patients (10) persisted with stable disease and 40 patients showed progressive disease. Although toxicities were more in the group. CT induction chemotherapy can thus support patients with locally advanced HNSCC by promoting appropriate chemoradiation regimens to improve control of disease.

Abbreviations

IC - Induction Chemotherapy, TPF - Taxane Platinum Fluorouracil, PF - Platinum Fluorouracil, RT – Radiation Therapy, CRT - Chemoradiotherapy, ORR - Overall Response Rate, OS - Overall Survival, PFS - Progression Free Survival, CT - Carboplatin Paclitaxel, HR - Hazard Ratio, LRC - Locoregional Control.

CONCLUSIONS

Reduction in tumour size after the treatment was compared in both the groups with RECIST 1.1. Induction chemotherapy caused significant reduction in tumour size but had more toxicities which were manageable. Response was better in patients with high nodal volume as some of the cases showed good response in the nodal volume irrespective of response of the primary. Hence, tumour biology of each and every patient is important in order to tailor the treatment accordingly under a multi-disciplinary team. When compared to conventional chemoradiation, induction chemo group did not show statistically significant benefit. Therefore, a more comprehensive study with a larger sample and longer duration of follow up is required.

This study emphasizes the role of induction chemotherapy in select patients with advanced disease, especially in high volume centres like MNJ Institute of Oncology and Regional Cancer Centre, where majority of cases (more than 80 %) are stage III or IV and above. Therefore, patient selection is the key to outweigh the risk involved.

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