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Original Research Article

A Prospective Randomised Trial Comparing Neoadjuvant Chemotherapy Followed by Concomitant Chemoradiation versus Concomitant Chemoradiation Alone in Locally Advanced Inoperable Head and Neck Squamous Cell Carcinoma

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ABSTRACT

Introduction: Concurrent chemoradiation is currently the standard of care in LAHNSCC. Neoadjuvant Chemotherapy (NACT) causes tumour down staging, facilitating organ preservation and has potential to prevent distant metastasis albeit at the cost of increased toxicities. However potential benefit of adding NACT before CTRT in LAHNSCC still remains unclear.

Aims and Objectives: This study compared NACT followed by CTRT versus CTRT alone in LAHNSCC in terms of Locoregional response (LRR), Toxicities and Progression Free Survival (PFS).

Materials and method: Patients with LAHNSCC of oral cavity, oropharynx, larynx & hypopharynx (AJCC Stage III-IVB), recruited from January 2013 to January 2015 were randomised into two arms (**90** each) to receive either NACT (Paclitaxel 175mg/m^2 and Carboplatin AUC 5 q 3 weeks 3 cycles) followed by CTRT (Arm A) or CTRT alone (Arm B). EBRT dose was 66–70 Gy in conventional fractionation with three weekly Inj. Cisplatin 100 mg/m^2.

Results: Median follow up period was 37 months. After NACT, 58.9% of patients achieved PR and CR 7.8%. Response 4 months after treatment showed LRR 56/65 in arm A vs. 53/71 in arm B. Median PFS was 48 months in Arm A vs. 42 months in Arm B; log rank p=0.176. Grade ≥ 3 acute toxicities included myalgia (10%), neutropenia (4.4 %), thrombocytopenia(3.3%) and anemia (3.3%) during NACT. During CTRT more haematotoxicities and mucositis in arm A whereas dermatitis and dysphagia were more in arm B. Regarding late toxicities, grade ≥ 3 neuropathy seen in Arm A.

Conclusion: NACT before CTRT is feasible and may be used in LAHNSCC to downstage tumour with no significantly added toxicity.

Key words: LAHNSCC, NACT, CR, PR, SD, PD

INTRODUCTION

Worldwide, annually, nearly 6,00,000 individuals are affected and more than 3,00,000 die of malignancies of the oral cavity, pharynx, and larynx. [1] Nearly 60% of this population presents with advanced disease i.e. stage III & IV. [2] Prognosis is quite poor for LAHNSCC- 40% to 60% of patients relapse and 30%-50% of patients live for less than 3 years

after treatment. [3] Among these patients approximately 50-60% of patients have local disease recurrence within 2 years, and 20-30% of patients develop metastatic disease. [4] Multiple trials established the superiority of CTRT over radiotherapy alone for LAHNSCC with improvement of progression free and overall survival. [5-8] This was conclusively proven in the MACH-NC meta-analysis with an absolute benefit of 6.5 % at 8 years over radiotherapy alone. [6] However, many patients present with extensive locoregional disease with overt symptoms. In them, NACT (induction chemotherapy, IC) can help to reduce the initial bulk of disease, thereby improving symptoms and quality of life and result in better organ preservation. [2,8,9] Nonetheless, different studies have observed that only CTRT relatively increases risk of distant metastases (15-20%). [4] On the other hand, NACT is beneficial in control of distant metastasis and achieving more chances of complete response (CR). [4,2,8,9]

Different trials had used PF (Cisplatin and 5-FU) as NACT before radiotherapy. Two phase III trials subsequently revealed benefits of adding Docetaxel (T) to PF as NACT before radiotherapy(TAX 323) or before CTRT (TAX 324) in terms of higher locoregional response, PFS and OS in TPF arm compared to PF arm in unresectable LAHNSCC. [2,10] Althou0gh most of the trials used Docetaxel in TPF regimen, one randomised trial by Hitt *et al.*(2004) shown significantly better CR rate, median TTF and OS in paclitaxel arm(PCF) vs. without Paclitaxel arm(CF). [11] Recently published DeCIDE and PARADIGM studies however did not show any statistically significant differences in OS, relapse Free Survival (RFS),Disease Free survival (DFS) or ORR between IC followed by CTRT versus CTRT alone in LAHNSCC with serious adverse events more common in the NACT arm. [12] Hence the utility of NACT and the optimal sequencing with radiotherapy remain unclear.

AIMS and OBJECTIVES

We conducted this study to test the effectiveness of paclitaxel and carboplatin based NACT followed by conventional CTRT in comparison to conventional CTRT alone in LAHNSCC in terms of locoregional response (primary end point), toxicity and progression free survival (two secondary end points) in patients of LAHNSCC.

MATERIALS AND METHODS

Study Design

In this prospective, randomized, open label, single-institutional phase II study, **180** patients of biopsy proven (oral cavity, oropharynx, larynx & hypopharynx) previously untreated LAHNSCC (AJCC group stage III, IVA and IVB) attending the Out Patient Department (OPD) of Radiotherapy, R.G. Kar Medical College and Hospital, Kolkata, were recruited from January 2013 starting to end of January 2015 and were randomised into two arms (90 each). Patients were included if they were 18-70 years, ECOG performance status of 0-1, normal baseline hematological and biochemical profiles (including hemoglobin ≥ 10 gm/dl, absolute neutrophil count ≥1,500 cells/mm^3, platelet count ≥100,000 cells/mm^3, serum creatinine clearance ≥ 45 ml/min, bilirubin ≤ 1.5 X Upper Limit of Normal, Liver Enzymes ≤ 2 X Upper Limit of Normal). Patients were excluded if they had already been treated, metastatic or recurrent disease, synchronous second primary or included in any other study. Cancer of the nasopharynx, paranasal sinuses, salivary glands, thyroid, orbit, external auditory canal and skin of head neck region were also excluded from the study. HPV titre determination was not mandatory in this study. The Institutional Ethical Committee approved the protocol. Written informed consent was obtained from all patients. The study was conducted in accordance with the International Conference on Harmonization Good Clinical Practise guidelines.

Treatment Protocol:

Eligible patients were randomized into two arms to receive either three cycles of NACT (with Inj. Paclitaxel 175 mg/m^2 IV infusion on day 1 over 180 minutes followed by Inj. Carboplatin AUC 5 IV on day 1 over 60 minutes and cycle repeated every 3 weeks) followed by conventional CTRT (Arm A; NACT-CTRT; Study arm, mentioned in the article as "Arm A" or "NACT") or conventional CTRT alone (Arm B; CTRT; Control arm, mentioned in the article as "Arm B" or "EBRT"). Secondary G-CSF prophylaxis was administered in case of Grade 2 or higher neutropenia and febrile neutropenia during NACT. Clinical and radiological evaluations were done by MRI 3 weeks after the last cycle of NACT in arm A and obvious cases of non progressive disease underwent further CTRT. All the patients in both arms underwent dental evaluation before irradiation. CTRT was administered with Inj. Cisplatin 100mg/m^2 IV on Day 1, 22 and 43 in both arms along with External Beam Radiation Therapy (EBRT) to a total dose of 66-70 Gy / 1.8-2 Gy per fraction to the Gross Tumour Volume (one fraction per day, and five fractions per week). Injection Carboplatin (typically AUC 2) was used instead of Cisplatin if creatinine clearance reduced to < 50 ml/min and if reduced to < 35 ml/min no concomitant chemotherapy was administered. Radiotherapy was delivered using CT simulation (GE Brivo, GE Inc., USA) by the Theratron 780 E Telecobalt machine and Theraplan Plus Treatment Planning System (both Theratronics International, Canada).

Response Assessment and Follow-Up

First follow up evaluation was scheduled at 2 weeks after completion of CTRT for assessment of acute toxicities and treatment tolerance. Next follow up schedule was 2 monthly for first 6 months, thereafter 3 monthly for next 2 years, then 6 monthly for upto 5 years and yearly thereafter. Each follow up evaluation included history, clinical and otorhinological examination and / or imaging as required. Chest radiography was performed yearly or if indicated. Locoregional assessment was done using the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 using MRI / CECT scan of head and neck 4 months and 1 year post treatment completion and as needed. Upon disease recurrence, patients were treated by the methods considered appropriate as decided by Multidisciplinary Tumour Board and mandated by the Departmental protocol.

Toxicity:

Toxicities were assessed using Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 in Arm A during NACT and in both arms during CTRT. Appropriate measures were taken for management of toxicities.

Statistical Analysis

Patients were randomly assigned to any of these two arms using computer generated random number sequencing. The two treatments groups were compared for baseline characteristics, response and toxicities using the Student's t test for continuous variables and chi square test for categorical variables. PFS was calculated in both arms according to the Kaplan-Meier survival curve and compared with the stratified log-rank test. PFS was calculated from the date of randomization to the date of disease progression or death from any cause or last follow-up (censored) and follow up period (using reverse Kaplan Meier analysis) was calculated from date of randomisation to last follow up (both in months). All reported p values were two-tailed and considered statistically significant if two-tailed $P < 0.05$

RESULTS AND ANALYSIS

The study was conducted between January 2013 to October 2019. Initially a total of 187 patients were randomized of which 3 patients in Arm A and 4 patients in arm B left before treatment starting. All baseline patient characteristics were comparable between the arms (p = Non Significant, NS) except baseline hemoglobin. (Tables 1, 2)

Table 1 : Baseline characteristics between two arms

Baseline characteristics*		Arm A(n= 90), n (%)	Arm B(n = 90), n (%)	P value
Gender	Male	68 (75.6)	59 (65.6)	0.14
	Female	22 (24.4)	31 (34.4)	
ECOG Performance status	0	18 (20)	18 (20)	1.0
	1	72 (80)	72(80)	
Subsite	Oral cavity	20 (22.2)	15(16.7)	0.15
	Oropharynx	31(34.4)	24(26.7)	
	Larynx	26(28.9)	26(28.9)	
	Hypopharynx	13(14.5)	25(27.7)	
Initial T Stage	T1	3 (3.3)	3 (3.3)	0.44
	T2	19 (21.1)	18(20)	
	T3	35 (38.9)	40 (44.5)	
	T4a	20 (22.2)	11 (12.2)	
	T4b	13(14.5)	18(20)	
Initial N Stage	N0	3 (3.3)	2 (2.2)	0.62
	N1	29 (32.3)	28 (31.1)	
	N2a	13 (14.4)	19 (21.1)	
	N2b	28 (31.1)	20 (22.2)	
	N2c	4 (4.4)	7 (7.8)	
	N3	13 (14.5)	14 (15.6)	
Initial stage Group	III	29 (32.2)	20 (22.2)	0.3
	IVA	35 (38.9)	38 (42.2)	
	IVB	26 (28.9)	32 (35.6)	
Differentiation (Grade)	Well	27 (30.0)	18 (20.0)	0.197
	Moderate	39 (43.3)	50 (55.6)	
	Poor	24 (26.7)	22 (24.4)	
LVSI	present	39 (43.3)	33(36.7)	0.36
PNI	present	21 (23.3)	25(27.8)	0.49
*Calculated for patients with :intention to treat".				

Table 2 : Baseline characteristics between two arms

Baseline characteristics		Arm A (n=90)	Arm B(n=90)	P value
Age (years)	Mean ±SD	51.4 ± 9.1	52.6 ± 8.5	0.353
	Median	51.5	53	
BSA (m^2)	Mean ±SD	1.59±0.13	1.56±0.12	0.100
BMI (Kg/m^2)	Mean ±SD	21.69±3.01	21.611±2.8	0.834
Hb (gm)	Mean ±SD	11.3 ±1.2	10.9±0.7	0.022*
Creatinine clearance(ml/min)	Mean ±SD	82.4±16.3	79.2±17.1	0.204
*statistically significant.				

Table 3 : Treatment parameters in both arms

Treatment parameters:

Treatment parameters		**Arm A [n(%)]**	**Arm B [n(%)]**	**P value**
Received all 3 cycles of NACT*		82/90 (91.1)	0(0)	NA
CTRT done (received a minimum dose of 45Gy or atleast 200mg/m^2 inj cisplatin or equivalent carboplatin)		76/82 (92.7)	82/90 (91.1)	0.707
Completed planned CTRT** (as per treatment protocol)		73/82 (89.02)	80/90 (88.9)	0.977
Mean dose of EBRT (Gy) Minimum dose Maximum dose		65.7 ± 2.31 55.8 68.4	66.3 ± 1.86 59.4 70.2	0.066
Median EBRT duration(days)		53	53	0.645
EBRT gap ≥ 5 days		20/76(26.3)	19/82(23.2)	0.649
Concurrent chemotherapy	*Cisplatin (3 cycles)*	76 /76 (100)	77 /82(93.9)	0.029
	Carboplatin (3/4 cycles)	0	5/82(6.1)	
Major causes of EBRT gap	*Hematotoxicity only*	2(2.6)	0(0)	0.531
	Dysphagia only	5(6.6)	5(6.1)	
	Dermatitis only	8 (10.5)	11(13.4)	
	Mucositis only	5(6.6)	3(3.7)	
	No gap	56(73.7)	63(76.8)	

**2 patients and 6 patients received 1 and 2 cycles of NACT respectively.*

***CTRT was started in 90 patients for EBRT arm (arm B) and in 82 patients in arm A (NACT arm).*

8 patients in Arm A (NACT ARM) did not start EBRT after NACT course. Of 82 patients started on CTRT treatment, 76 patients finished the CTRT course (73 completed CTRT and 3 patients did not complete the prescribed treatment, either inadequate EBRT dose or number of concurrent chemotherapy cycles or due to disease progression.6 patients declined any further concurrent chemotherapy or did not receive minimum 45 Gy EBRT dose or stopped treatment due to grade 3 or more adverse events and hence left out of response assessment.

10 patients in Arm B (EBRT arm) did not complete the said treatment protocol which included 8 patients whose were lost during treatment i.e did not receive minimum 45Gy EBRT dose for microscopic disease control or stopped treatment due to grade 3 or more adverse events and and 2 patients received inadequate EBRT DOSE.

***Completed CTRT course** was defined as GTV dose of 66-70Gy and number of concurrent cisplatin 3 cycles or carboplatin 6 cycles or as appropriate after cisplatin withdrawal.*

Efficacy outcomes:

In Arm A, after NACT, maximum patients (58.9 %) achieved PR (CR=7.8 %, SD=22.2 %, PD=2.2 %). Two disease progression occurred during NACT in arm A

Table 4: Locoregional Response after NACT in arm A

Response after NACT	n=90, n(%)
CR	7 (7.8)
PR	53(58.9)
SD	20(22.2)
PD	2(2.2)
Others(lost)	8(8.9)

8 patients in arm A after completion of NACT did not proceed for CTRT. 82 patients in arm A and 90 patients in arm **B** were started on CTRT of which only 76 patients in arm A and 82 patients in arm B finished CTRT respectively. However four months after treatment completion, 86.2% patients achieved CR in arm A(n=65) vs. 74.6 % in arm B(n=71) (p=NS). Three progressions took place in arm A all locoregional and eight progression in arm B including five locoregional progression.

Table 5 : Locoregional Response at 4 months post treatment

Response at 4 months after treatment	Arm A(n = 65), n (%)	Arm B (n = 71), n (%)	P value
CR	56(86.2)	53(74.6)	0.213
SD	6(9.2)	10(14.1)	
PD	3(4.6)	8(11.3)	

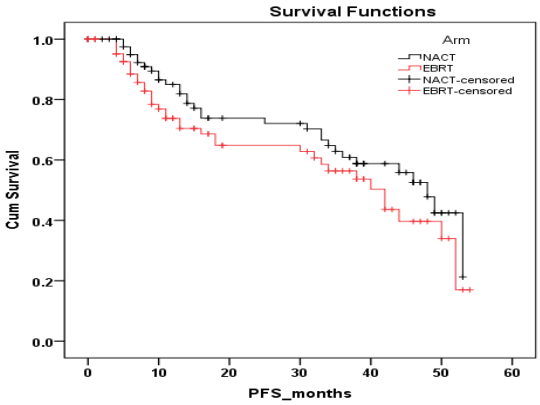

Figure 1 : Comparison of PFS between both the arms.

Table 6A. Means and Medians for Survival Time – comparison of Progression Free Survival in months

Means and Medians for Survival Time – comparison of Progression Free Survival in months								
Arm	Mean[a]				Median			
	Estimate	Std. Error	95% Confidence Interval		Estimate	Std. Error	95% Confidence Interval	
			Lower Bound	Upper Bound			Lower Bound	Upper Bound
NACT	37.999	2.241	33.606	42.392	48.000	2.950	42.217	53.783
EBRT	33.790	2.433	29.021	38.559	42.000	4.748	32.694	51.306
Overall	36.039	1.661	32.784	39.294	44.000	4.261	35.648	52.352
a. Estimation is limited to the largest survival time if it is censored.								

Median follow up period (calculated by reverse Kaplan Meier analysis) were 38 months (mean ± SD 30.99 ±2.088 months) in Arm A vs 34 months (28.33±2.27 months) in Arm B. Median PFS (compared by Kaplan Meier Survival analysis) between these 2 arms based on "intent to treat" did not differ significantly although a trend towards improved PFS in Arm A was seen (Arm A 48.0 months vs. 42.0 months in Arm B; log rank p = 0.176). There were total of 31 events (progression or death due to any cause) in arm A (including 11 deaths of which six due to disease progression, one due to treatment related toxicity and rest four due to other causes) versus 36 events in

arm B (including 15 deaths with ten due to disease progression & five other causes) till July 2019.(figure 1 and table 6A)

PFS was also calculated with patients who had "received treatment" which included patients who "completed treatment as per treatment protocol". It is to be emphasized that "received treatment" was defined as patients who received EBRT 45 Gy and above and minimum cumulative dose of 200mg/m^2 of inj cisplatin. Table 6B highlighted no difference in PFS for this subset analysis.

Table 6B. PFS in months for patients who "received treatment".

Means and Medians for Survival Time – PFS in months									
CTRT_ RECEIVED	Arm	Mean[a]				Median			
		Estimate	Std. Error	95% Confidence Interval		Estimate	Std. Error	95% Confidence Interval	
				Lower Bound	Upper Bound			Lower Bound	Upper Bound
Yes	NACT	35.346	1.989	31.447	39.244	39.000	1.994	35.092	42.908
	EBRT	31.048	2.284	26.571	35.525	36.000	2.640	30.826	41.174
	Overall	33.208	1.516	30.237	36.179	38.000	.938	36.161	39.839
Overall	Overall	33.208	1.516	30.237	36.179	38.000	.938	36.161	39.839
Estimation is limited to the largest survival time if it is censored. Log rank test , p value 0.449.									

Table 7A. Adverse events during NACT, n=90.

Adverse events during NACT		Count	Column N %
ANEMIA_NACT_all grades	NO	62	68.9%
	YES	28	31.1%
ANEMIA_NACT_G3	NO	87	96.7%
	YES	3	3.3%
NEUTROPENIA_NACT_ all grades	NO	63	70.0%
	YES	27	30.0%
NEUTROPENIA_NACT_G3	NO	86	95.6%
	YES	4	4.4%
THROMBOCYTOPENIA_NACT_ all grades	NO	79	87.8%
	YES	11	12.2%
THROMBOCYTOPENIA_NACT_G3	NO	87	96.7%
	YES	3	3.3%
MYALGIA_NACT_ all grades	NO	65	72.2%
	YES	25	27.8%
MYALGIA_NACT_G3	NO	81	90.0%
	YES	9	10.0%
DIARRHEA_NACT_ all grades	NO	84	93.3%
	YES	6	6.7%
DIARRHEA_NACT_G3	NO	88	97.8%
	YES	2	2.2%

Table 7B : Comparison of toxicities between two Arms during CTRT

Adverse events	Arm A (n = 82), n (%)		Arm B (n=90), n (%)		P value
	All Grade	Grade ≥ 3	All Grade	Grade ≥ 3	(only ≥G3)
Anemia	13(15.9)	3 (3.7)	11(12.2)	0 (0)	0.067
Neutropenia	15(18.3)	4 (4.9)	4(4.4)	1 (1.1)	0.142
Thrombocytopenia	8(9.8)	3 (3.7)	2(2.2)	0 (0)	0.067
Dermatitis	43(52.4)	8 (9.8)	52(57.8)	11 (12.2)	0.606
Mucositis	41(50)	7 (8.5)	27(30)	5 (5.6)	0.443
Dysphagia	31(37.8)	6 (7.3)	39(43.3)	7 (7.8)	0.909
Neuropathy	11(13.4)	2 (2.4)	3(3.3)	0 (0)	0.136
Subcutaneous fibrosis	17(20.7)	4 (4.9)	16(17.8)	5 (5.6)	0.842
Xerostomia	32(39.0)	10 (12.2)	37(41.1)	12 (13.3)	0.823

Toxicity outcomes:

In arm A during NACT (n=90), myalgia (10%), neutropenia (4.4%) followed by thrombocytopenia (3.3%), anemia (3.3 %) and diarrhoea (2.2 %) appeared as grade ≥3 acute toxicities. Peripheral neuropathy grade 1/2 symptoms was complained in only 7 patients. (Table 7A) During CTRT, numerically more grade ≥ 3 haematotoxicities and mucositis seen in arm A (n=82, who were started on CTRT) whereas dermatitis and dysphagia were

more in arm B (n=90, who were started on CTRT). Nineteen patients in arm A and 20 patients in arm B had treatment related gap of 5 or more days during CTRT due to grade 3 or more dysphagia ,mucositis, dermatitis and haematotoxicities. Regarding late toxicities, grade ≥ 3 neuropathy seen in Arm A but xerostomia and subcutaneous fibrosis were noted more in Arm B (statistically not significant).

DISCUSSION

The rationale behind the use of induction treatment was based upon two hypotheses - better delivery of the drug in untreated, well-vascularised tumours and eradication of the micro metastatic disease. [4] There is no method to assess prognosis and adjust treatment intensity once CTRT has started. For these reasons combining NACT with CTRT as sequential therapy has a strong biologic rationale and thus ongoing clinical trials are testing this approach. [13]

Role of CTRT as an effective treatment option in inoperable LAHNSCC has been proved long back. [14,15] CTRT significantly improved 5 years disease specific survival and locoregional control rates in advanced stage oropharyngeal cancers without significantly increased severe late morbidity. [16] A trial by Forastiere *et al.* in 547 locally advanced laryngeal cancer patients also demonstrated significantly better larynx preservation and locoregional control with CTRT than sequential chemo & radiotherapy or radiotherapy only. [5] A meta-analysis of 93 trials in over 17,346 patients (Meta-Analysis of Chemotherapy on Head and Neck Cancer [MACH-NC]) demonstrated 19 % & 4% reduction in risk of death with CTRT and NACT followed by RT arms respectively and an overall 6.5 % and 2.4% improvement in 5 year survival with CTRT and NACT followed by RT arms respectively compared to RT alone arms. Loco-regional failure was significantly less with CTRT. [6,16] After the publication of this meta-analysis CTRT became the standard of treatment in LAHNSCC.

Different trials have also used Injection Cisplatin and 5-FU (PF) as NACT before radiotherapy. Two phase III trials (TAX 323 or EORTC 24971 and TAX 324) subsequently revealed benefits of adding Docetaxel (T) to PF as NACT before radiotherapy. The TAX 323 trial revealed significantly higher ORR, PFS and OS with TPF arm in unresectable LAHNSCC compared to PF arm. However there were more grade 3 or 4 leucopoenia and neutropenia in TPF arm and thrombocytopenia and stomatitis in PF arm. [2] The TAX 324 trial also compared TPF with PF prior to CTRT over 501 patients of LAHNSCC. Median OS, PFS and locoregional control were significantly better in the TPF arm. Grade 3 or higher neutropenia and thrombocytopenia were significantly higher in the TPF & PF arms respectively. [10] The long-term results of TAX324 came out with median follow-up period of 72·2 months which also showed significantly better OS and PFS with TPF. [17]

Qin *et al.* published meta-analysis of four RCTs (randomised controlled trials), which included 1,552 patients with LAHNC comparing TPF vs. PF before CTRT. The 3-year PFS,OS and overall response to chemotherapy were significantly better in TPF arm whereas febrile neutropenia was also significantly higher in the TPF group, though it was manageable. [18] Another meta-analysis of five randomized trials (representing 1,772 patients) by Blanchard *et al.* in 2013 with median follow-up of 4.9 years also revealed significant reductions of progression, locoregional failure and distant failure with TPF compared with PF before radiation. [19]

Thus it became quite obvious to use TPF instead of PF as NACT before radiation, but still the question remains unanswered whether NACT is at all needed before CTRT. To answer this question, numerous trials started. A phase III trial by R. Hitt over 439 LAHNSCC patients, demonstrated that NACT followed by CTRT significantly increases TTF (time to

treatment failure) and loco regional control compared with CTRT alone. [9] Another study by Paccagnella *et al.* over 101 patients of LAHNSCC, CR rates were significantly better with TPF followed by CTRT compared to CTRT alone with no negative impact on CTRT feasibility in NACT arm. Hematologic and non-hematologic toxicities during CTRT were similar in both arms. [8] A phase III factorial study by Ghi *et al.* compared CTRT or cetuximab/RT (CET/RT) versus induction TPF followed by CTRT or CET/RT in patients with LASCCHN. There was significant improvement of radiological CR,3 year PFS and 3 year OS in favour of both induction arms than both concomitant arms without compromising treatment compliance. [20]

On the contrary, a retrospective analysis by Balerampas *et al.* in 2014 comparing IC followed by CTRT vs. CTRT alone over 83 patients, OS was significantly higher in CTRT arm. [21] Another Phase III randomized trial by Hitt *et al.* failed to demonstrate any statistically significant differences for median PFS, OS and median TTF among patients received TPF followed by CTRT , PF followed by CTRT and CTRT alone arm. [22] Another randomized phase II study by Takácsi-Nagy *et al.* over 66 patients with stage III or IV unresectable HNSCC also did not reveal any significant differences in rate of radiologic CR,OS and PFS in ICT plus CTRT over CTRT group whereas grade 3–4 neutropenia was significantly higher in induction arm. [23] In our study we found no significant difference between Induction arm and CTRT only arm in terms of LRR at 4 months completion and also for median PFS.

The recently published DeCIDE trial [12] also did not show any statistically significant differences in OS, relapse Free Survival (RFS), Disease Free survival (DFS) or ORR between IC followed by CTRT versus CTRT over 285 non metastatic N2 or N3 HNSCC patients although serious adverse events were more common in the NACT arm. The study was criticized as underpowered because it did not meet the planned accrual target. A similar phase III trial by Haddad *et al.* (PARADIGM study) over 145 patients compared the use of TPF IC followed by CTRT with CTRT alone in LAHNSCC patients. Three-year OS and PFS did not differ significantly between the arms. More patients had febrile neutropenia in NACT-CTRT arm. [14-24] However, both DeCIDE and PARADIGM studies neither used standard cisplatin based concomitant agent in NACT arm. Therefore, the true feasibility and improvement of adding induction to the current cisplatin-based standard of care may remain unclear and still be a lingering question. [25]

In a meta-analysis by Zhang *et al.* of 5 RCTs with 922 patients compared CTRT alone versus IC followed by CTRT which did not show statistically significant differences in OS, PFS, ORR or locoregional recurrence rate (LRR) between the arms. However significantly increased grade 3 or higher neutropenia and leucopoenia found in CTRT only arm whereas significantly decreased distant metastasis rate and improved CR found for IC f/b CTRT arm. [3] In our study, Grade ≥ 3 toxicities included numerically more haematotoxicities, mucositis and neuropathy in Induction arm and dermatitis, dysphagia, xerostomia and subcutaneous fibrosis in CTRT only arm (statistically non-significant).

Another meta-analysis of 5 trials by Budach W *et al.* over 1022 patients with LAHNSCC also did not demonstrate any significant difference of OS and PFS between IC followed by CTRT vs. CTRT alone however, concomitant chemotherapy regimen varied in different trials. [26]

Most of the trials used Docetaxel in TPF regimen but in our study we have used Paclitaxel. Similar regimen has been used in a randomised trial by Hitt *et al.(*2004) over 382 patients.CR rates and median TTF were significantly better in Paclitaxel arm (PCF) vs. without Paclitaxel arm(CF). [11]

Although 5-FU is an integral part of the TPF regimen, it is commonly associated

with mucositis which overlaps with the toxic effects expected with CTRT, and may delay or impair RT delivery during definitive RT. An alternative strategy would be platinum with taxanes only omitting 5FU. [25] There are few trials where paclitaxel-carboplatin only were used as NACT, although most of the trials are single arm study and some are on recurrent and metastatic setting. A phase II trial by Machtay *et al*. over 53 technically resectable stage III/IV SCC of the oropharynx were treated with paclitaxel and carboplatin based NACT followed by definitive CTRT.90% patients had CR after CTRT. Three-year event-free survival was 59% and Organ preservation was achieved in 77% patients whereas treatment-related mortality rate was only 4%. [27]

Another single arm trial by Dunphy *et al.*(Paclitaxel and Carboplatin based NACT followed definitive RT in newly diagnosed advanced HNC with 74 % Stage IV disease) shown complete plus partial response 61-76% and organ preservations 39- 59% whereas another single arm study by Fornari *et al.* (paclitaxel and carboplatin based NACT before definitive CTRT in LAHNSCC) demonstrated CR+PR: 90.8% for T stage and 75% for N stage. [28,29] Other two phase II studies by Fountzilas *et al.* and Clark *et al.* demonstrated use of paclitaxel and carboplatin in recurrent and metastatic HNC with good response. [30,31]

Another single arm trial by Vokes *et al* with Paclitaxel-Carboplatin based NACT before definitive CTRT showed significant reduction in mouth and throat pain with 83% CR after treatment completion. Overall 3-year PFS was 80% and OS 70%. [32]

However our study had limitations like small sample size, single institutional and non-availability of IMRT radiation techniques.

CONCLUSION

Our study demonstrates that Paclitaxel and Carboplatin based NACT before CTRT is feasible and can be of some potential benefit in patients with LAHNSCC especially to downstage tumour thereby decreasing symptoms with a trend towards improved treatment response and PFS without substantial added toxicity.

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