Conventional chemoradiation vs. induction chemotherapy followed by conventional chemoradiation for locally advanced head and neck cancer: A prospective, randomized study

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Received May 28, 2020; Accepted August 24, 2020

DOI: 10.3892/wasj.2020.65

Abstract. The standard-of-care in locally advanced squamous cell carcinoma of the head and neck (LA SCCHN) remains concurrent chemoradiotherapy. The present study compared the disease response and safety profile of induction chemotherapy followed by concomitant chemoradiotherapy (CRT) vs. CRT alone in patients with LA SCCHN. The present prospective randomized study was conducted between July, 2014 and July, 2015 on 52 patients with SCCHN of the oropharynx, hypopharynx and larynx. Patients were randomly divided into the induction chemotherapy [docetaxel, cisplatin and 5-FU (TPF)] followed by CRT arm (TPF + CRT arm, n=25) or the CRT alone arm (CRT arm, n=27). The disease response, and acute and late toxicities were assessed. At the first follow-up (6 weeks), the overall response rate (ORR) was 82.6% for the TPF + CRT arm and 72% for the CRT arm; the difference was not significant. In addition, no statistically significant differences were observed in the nodal response between the treatment arms. Acute toxicities were significantly higher in the TPF + CRT arm, with respect to mucositis and hematological toxicities. No differences were observed in late-onset toxicities observed following 3 months of radiotherapy. Triple drug-based sequential therapy was tolerable in the population in the present study and may thus hold promise for the treatment of SCCHN; however, larger prospective studies are required to confirm these results.

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Key words: induction chemotherapy followed by chemoradiotherapy, chemoradiotherapy, induction chemotherapy, head and neck cancer, squamous cell carcinoma of the head and neck

Introduction

Head and neck cancer is the sixth most common type of cancer worldwide (1), with ~500,000 new cases diagnosed annually. It constitutes 5% of all cancer cases worldwide. In India, head and neck cancer accounts for 29.6% of all cancer cases among males (range, 24.3-34.3%) and 11.84% of all cancer cases among females (range, 10.5-15.5%) as per different hospital-based registries (2,3). Squamous cell carcinoma of the head and neck (SCCHN) constitutes >90% of all head and neck cancers (1). In India, SCCHN arising from the oral cavity is the most common type of cancer among males and the third most common type among females (1,4). Approximately, 16% of all cancer cases were registered as SCCHN at the Regional Cancer Centre, Indira Gandhi Medical College, Shimla, India, from 2001 to 2010, accounting for 10.6% of all cancer cases among males and 5.4% of all cancer cases among females (unpublished data). The geographic distribution reveals a very large variation in the incidence of head and neck cancers in different countries, with low incidences reported in Western Europe and high incidences in South Asia, parts of Africa and South America (5).

The incidence of early-stage SCCHN (stage I or II) is ~40%, whereas 60% of cases are reported with locally advanced (stages III and IVA/B) and metastatic (stage IVC) disease (6). Therapeutic options for early-stage SCCHN include both surgery and radiotherapy as a single treatment modality, with a cure rate of ~80% (6,7). Radiotherapy alone has long been the standard non-surgical therapy for locally advanced disease (8,9). A previous meta-analysis of individual patient data from >10,000 participants in 63 trials [Meta-Analysis of Chemotherapy on Head and Neck Cancer (MACH-NC)] demonstrated that the addition of chemotherapy to radiotherapy in both definitive and adjuvant postoperative settings resulted in a 12% reduction in the risk of mortality from head and neck cancer, corresponding to an absolute improvement of 4% in the 5-year survival rates (10).

The use of induction chemotherapy followed by radiotherapy has resulted in organ preservation without compromising overall survival, when compared with radiotherapy alone in the

treatment of SCCHN (11). Previously, 2 phase III TAX323 (12) and TAX324 (13) trials demonstrated the efficacy of induction chemotherapy [TPF (docetaxel and cisplatin, day 1; fluorouracil by continuous infusion, days 1 to 5)] plus radiotherapy for the treatment of patients with locally advanced (LA) unresectable SCCHN with overall response rates (ORRs) of 68% and 72%, respectively. The aforementioned studies revealed that a therapeutic gain may be achieved in patients with SCCHN when concomitant chemoradiotherapy is preceded by induction chemotherapy. Hence, the present study compared induction chemotherapy followed by concomitant chemoradiotherapy (CRT) vs. CRT alone in Indian patients with LA SCCHN.

Materials and methods

Study population. Patients of either sex, aged ≤70 years with a histologically confirmed diagnosis of stage IVA/B SCCHN of the oropharynx, hypopharynx and larynx, who were previously untreated and had a Karnofsky performance status score of >70, were included in the present study. The key exclusion criteria were the following: A histology other than SCCHN, hemoglobin (Hb) levels ≤10 gm%, deranged liver and renal function tests and the presence of distant metastasis.

Study design. The present study was a prospective, randomized two-arm study conducted between July, 2014 and July, 2015. The patients (n=52) were randomly divided by stratification into 2 treatment groups/arms: The induction chemotherapy (docetaxel, cisplatin and 5-FU) followed by CRT arm (TPF + CRT arm; n=25) and the conventional CRT alone arm (CRT arm; n=27). Randomization was carried out by stratification, and the treatment assignment was stratified according to the site of disease (hypopharynx, larynx or oropharynx), N stage (node -ve or +ve) and T stage (T1 and T2 vs. T3 and T4). Patients were randomly divided into the TPF + CRT arm and CRT arm based on the treatment they received. Approximately equal numbers of patients were assigned to each group.

Study treatments

TPF + CRT arm. Patients randomly divided into the TPF + CRT arm were administered induction chemotherapy with docetaxel (75 mg/m^2) on day 1, and cisplatin (75 mg/m^2) and 5-FU (750 mg) on days 1 and 2 in 3 weekly cycles for a total of 3 cycles. Granulocyte-colony stimulating factor (G-CSF; Filgrastim, 300 μg) was administered prophylactically on day 3 of each cycle. Dexamethasone (16 mg), ranitidine (50 mg), chlorpheniramine maleate (5 mg) and ondansetron (8 mg) were administered in each cycle. Dose modifications were allowed as follows: i) The dose of docetaxel was reduced after any episode of febrile neutropenia, grade 4 neutropenia (lasting >5 days), grade 4 thrombocytopenia, or >grade 3 asthenia; ii) The dose of cisplatin was reduced to 75% of the original dose in subsequent cycles if any of the following occurred: >grade 3 sensory neurotoxicity, ≥grade 2 nephrotoxicity, persistent grade 4 neutropenia or neutropenic fever following the dose reduction of docetaxel; iii) The dose of 5-FU was reduced by 25% in any of the following circumstances: For patients with grade 3 diarrhea lasting for >7 days despite the administration of loperamide, mucositis grade 3 lasting for >5 days, or grade 4 mucositis.

Following 3 cycles of induction chemotherapy, concurrent CRT with cisplatin (30 mg/m^2) on day 1 of each week and conventional radiotherapy daily with 2 Gy fraction for 5 days a week for a total of 6½ weeks (total, 66 Gy/6½ weeks/33#) were administered (Fig. 1A).

CRT arm (conventional CRT). Patients assigned to the CRT arm received standard concomitant CRT with cisplatin (30 mg/m^2) on day 1 of each week for 7 doses and conventional radiotherapy daily with a 2 Gy fraction for 5 days a week for a total of 6½ weeks (total, 66 Gy/6½ weeks/33#). G-CSF (Filgrastim, 300 μg) was administered only if necessary, after reviewing the investigations, not prophylactically (Fig. 1B).

Study assessments. The first follow-up was performed at 6 weeks following treatment and subsequent follow-ups were performed every 2 months. The primary endpoint was the response rate (RECIST 1.1) at 6 weeks as evaluated by the following criteria: i) Complete response (CR): A complete regression of the lesion (primary, as well as neck nodes); ii) Partial response (PR): A >50% regression in the lesion in maximal diameter; iii) Stable disease: If the lesion regressed <50% in maximal diameter; and iv) Progressive disease: If the lesion increased by 25% or the appearance of a new lesion or secondary metastatic disease were noted.

Toxicity profiles were evaluated each week during treatment and at the end of treatment. The toxicity was assessed according to the Radiation Therapy Oncology Group toxicity criteria (14). Treatment toxicities occurring within 90 days of the commencement of radiotherapy were considered acute and those occurring or persisting >90 days after the commencement of radiotherapy were considered as late.

Statistical analysis. Quantitative data are presented as the means and standard deviation, and qualitative data by frequency and distribution. The Student's t-test and χ^2 test were used for the statistical comparisons of parametric data. Statistical significance was considered as follows: P>0.05 as non-significant, P=0.05-0.01 as significant and P<0.01 as highly significant. SPSS (version 24) was used for statistical analysis.

Results

Patient disposition and demographics. Of the 52 patients enrolled in the present study, 25 were randomized to the TPF + CRT arm and 27 to the CRT arm (Fig. 2). The median age of the patients was 56.2 years. The patients were followed-up for a median duration of 4 months. The baseline characteristics (Table I) of the study participants did not differ significantly between the 2 study arms. The present study was conducted after due approval from the Institutional Ethics Committee, Indira Gandhi Government Medical College (IGMC), Shimla, Himachal Pradesh, India. All the patients provided written informed consent for participation.

Treatment efficacy. In total, 2 patients in the TPF + CRT and CRT group (in each group) were lost to follow-up. The ORR was 82.6% [CR, 78.3% (18/23); PR, 4.3% (1/23)] for the TPF + CRT arm and 72% [CR, 64% (16/25); PR, 8% (2/25)] for the CRT arm at the first follow-up (Fig. 3). No significant differences

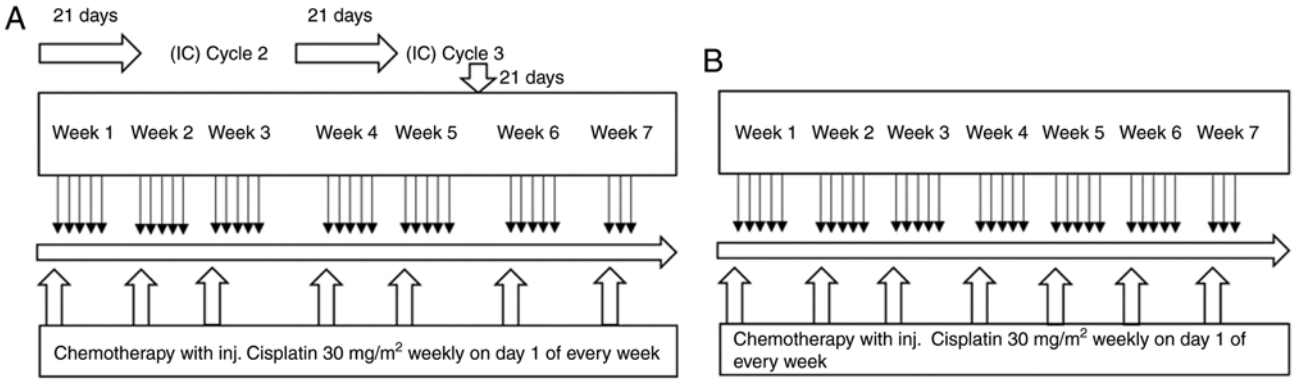

Figure 1. Study design. (A) TPF + CRT arm, (B) CRT arm. In the TPF + CRT arm, following 3 cycles of induction chemotherapy, concurrent chemoradiotherapy with cisplatin (30 mg/m^2) on day 1 of each week and conventional radiotherapy daily with 2 Gy fraction for 5 days a week for a total of 6½ weeks (total, 66 Gy/6½ weeks/33#) were administered. In the CRT arm, standard concomitant CRT with cisplatin (30 mg/m^2) on day 1 of every week for 7 doses and conventional radiotherapy daily with 2 Gy fraction for 5 days a week for a total of 6½ weeks (total, 66 Gy/6½ weeks/33#) were administered. TPF + CRT, induction chemotherapy [TPF (docetaxel and cisplatin, day 1; fluorouracil by continuous infusion, days 1 to 5)] plus radiotherapy; CRT, concomitant chemoradiotherapy alone.

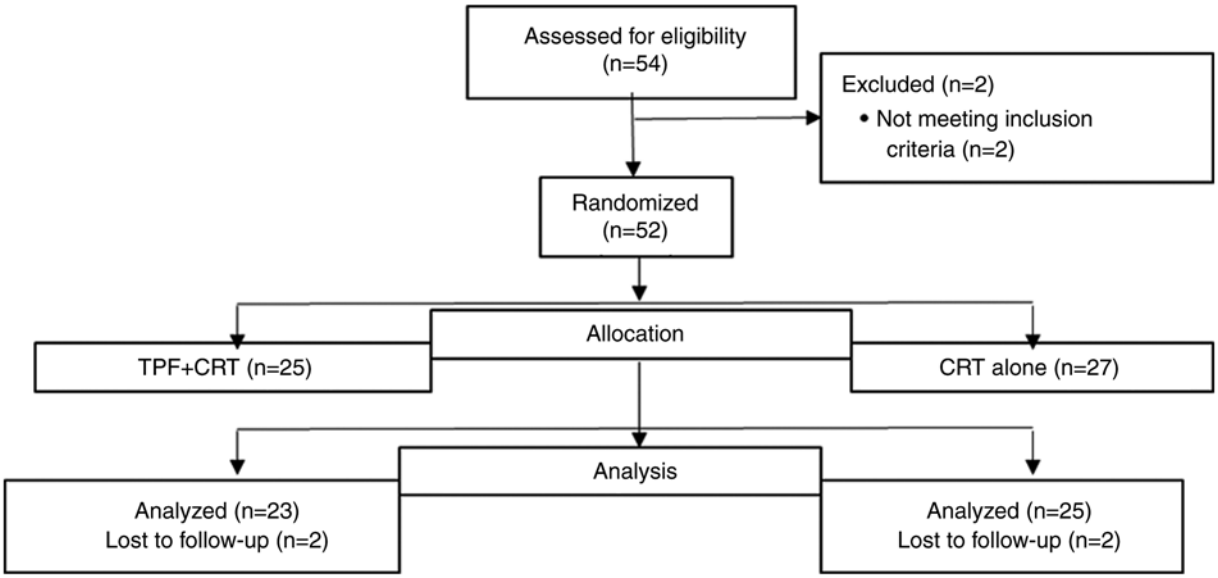

Figure 2. CONSORT flow diagram. Of the 52 patients enrolled in the present study, 25 were randomized to the TPF + CRT arm and 27 were randomized to the CRT arm. TPF + CRT, induction chemotherapy [TPF (docetaxel and cisplatin, day 1; fluorouracil by continuous infusion, days 1 to 5)] plus radiotherapy; CRT, concomitant chemoradiotherapy alone.

(P=0.999) were observed in disease response at the primary site in both study arms. Disease progression was reported in 1 patient in each arm. The response was not evaluated in 3 and 4 patients in the TPF + CRT and CRT arms, respectively.

For nodal response, the ORR was 82.6% [CR, 73.9% (17/23); PR, 8.7% (2/23)] for the TPF + CRT arm vs. 76% [CR, 56% (14/25); PR, 20% (5/25)] for the CRT arm. No statistically significant differences were observed in nodal response between the treatment arms at the first follow-up.

At the median follow-up of 3.5 months, 17 (73.9%) patients in the TPF + CRT arm and 15 (60%) patients in the CRT arm achieved CR (P=0.307). Similarly, complete nodal response at the median follow-up of 3.5 months was achieved in 16 (69.6%) and 13 (52%) of the patients in the TPF + CRT and CRT arms, respectively (P=0.367).

No statistically significant differences were found in CR in both the treatment arms when analyzed for different subgroups: Sex, smoking status, alcohol status, smoking and alcoholic status, diet, cancer site and cancer stage. A trend for a better response with TPF + CRT was observed across cancer sites (oropharynx, larynx and hypopharynx) and cancer stages (IVA and IVB), although the difference was not statistically significant (Table II).

Safety. During treatment, majority of the patients suffered from grade 3 skin toxicity, which was higher with TPF + CRT as compared to CRT (65.2 vs. 48%; P=0.262). Grade 3 mucositis was significantly (P=0.016) higher in the patients in the TPF + CRT arm (52.2%) compared to those in the CRT arm (16%). Grade 2 laryngeal toxicities were observed in the majority of patients, including hoarseness or whispered speech, throat pain and cough. Grade 2 and 3 pharyngeal toxicities combined were higher in the CRT (grade 2, 64%; grade 3, 24%) vs. the TPF + CRT arm (grade 2, 60.7%; grade 3,

Table I. Baseline characteristics of the study participants.

Parameter	TPF + CRT (n=25)	CRT (n=27)
Age, mean, years	54.9	60.7
Median	56	60
Range	37-70	45-70
31-40 years, n (%)	1 (4)	0
41-50 years, n (%)	6 (24)	6 (22.2)
51-60 years, n (%)	7 (28)	8 (29.6)
61-70 years, n (%)	11 (44)	13 (48.2)
Sex, n (%)		
Male	23 (92)	26 (96.3)
Female	2 (8)	1 (3.7)
Smoker, n (%)	22 (88)	26 (96.2)
Alcohol consumption n (%)		
Chronic alcohol consumption	8 (32)	13 (48.1)
Occasional alcohol consumption	9 (36)	10 (37.1)
No alcohol consumption	8 (32)	4 (14.8)
Karnofsky performance status, mean (range)	87.6 (80-90)	85.9 (80-90)
Hemoglobin levels (g/dl), mean	12.9	12.7
Cancer sites, n (%)		
Oropharynx	15 (60)	14 (51.9)
Larynx	7 (28)	7 (25.9)
Hypopharynx	3 (12)	6 (22.2)
Cancer subsites, n (%)		
Vallecula	6 (24)	6 (22.2)
Base of tongue	7 (28)	4 (14.8)
Supraglottis	5 (20)	5 (18.5)
Tonsil	2 (8)	4 (14.8)
Pyriform sinus	2 (8)	4 (14.8)
Glottis	2 (8)	2 (7.4)
Lateral pharyngeal wall	1 (4)	1 (3.7)
Posterior pharyngeal wall	0	1 (3.7)
T stage, n (%)		
T1	2 (8)	2 (7.4)
T2	10 (40)	8 (29.6)
T3	6 (24)	8 (29.6)
T4	7 (28)	9 (33.3)
N stage, n (%)		
N0	2 (8%)	3 (11.1%)
N1	3 (25%)	4 (14.81%)
N2	17 (68%)	18 (66.7%)
N3	3 (12%)	2 (7.4%)
Cancer stage, n (%)		
IVA	20 (80)	22 (81.5)
IVB	5 (20)	5 (18.5)

P-value >0.05 for all parameters between the 2 groups. TPF + CRT, induction chemotherapy [TPF (docetaxel and cisplatin, day 1; fluorouracil by continuous infusion, days 1 to 5)] plus radiotherapy; CRT, concomitant chemoradiotherapy alone.

17.4%), although no significant differences were observed. Significantly higher grade 3 hematological toxicities were observed in the TPF + CRT vs. the CRT arm (60.9 vs. 24%, P=0.012). Gastrointestinal toxicity was slightly higher in the TPF + CRT (28%) vs. the CRT (25.9%) arm. Febrile neutropenia was observed in 1 (4%) patient receiving TPF + CRT.

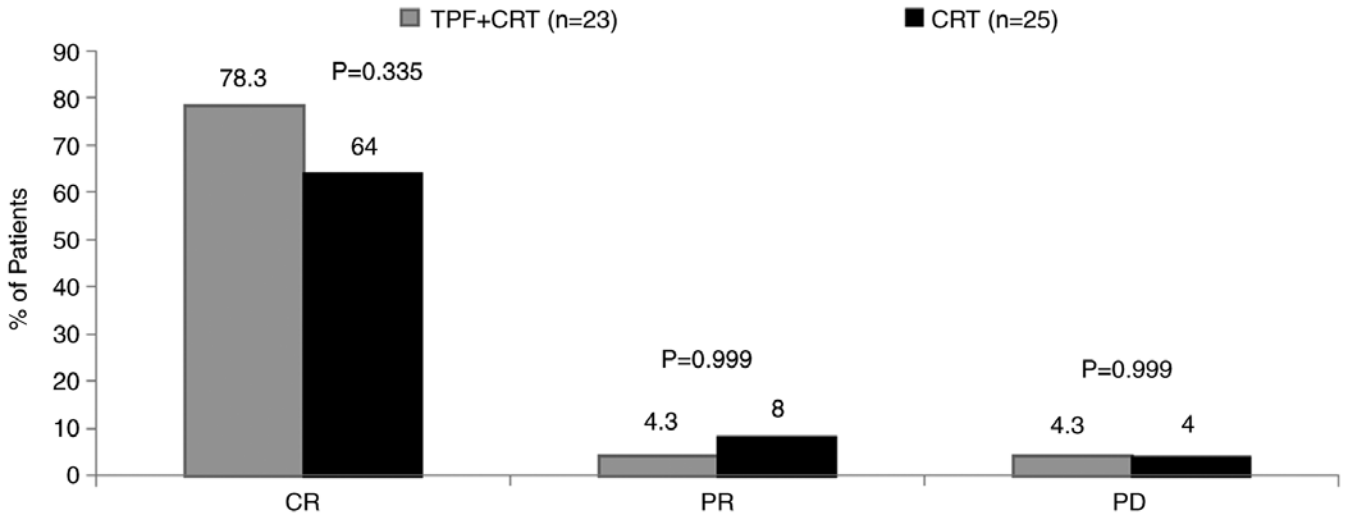

Figure 3. Efficacy evaluation for TPF + CRT vs. CRT arms at first follow-up. χ^2 tests were used for statistical comparisons of the parametric data. Statistical significance was as follows: P>0.05 as non-significant, P=0.05-0.01 as significant and P<0.01 as highly significant. CR, complete response; PD, progressive disease; PR, partial response; TPF + CRT, induction chemotherapy [TPF (docetaxel and cisplatin, day 1; fluorouracil by continuous infusion, days 1 to 5)] plus radiotherapy; CRT, concomitant chemoradiotherapy alone.

Treatment interruptions (TPF + CRT, 40%; CRT, 37%) were observed as follows: TPF + CRT arm: Due to grade 3 and 4 skin toxicity, grade 3 and 4 mucositis and hematological toxicity; CRT arm: Due to the withdrawal of consent and 1 patient leaving the treatment in between.

Toxicity at first follow-up. In the TPF + CRT arm, 65.2% of the patients had grade 1 salivary gland toxicity compared with 36% patients in the CRT arm. Skin reactions occurring during the treatment were healed at first follow-up. Mucositis was not healed in 1 patient (4.34%) in the TPF + CRT arm and 2 patients (8%) in the CRT arm. The majority of the patients had grade 1 salivary gland toxicity (Table III).

Late skin toxicity, depigmentation. Depigmentation was present in 16 (69.6%) of the patients in the TPF + CRT arm compared with 14 (56%) of patients in the CRT arm. Subcutaneous fibrosis was present in 13% of the patients in the TPF + CRT arm compared with 12% in the CRT arm (Table III).

Discussion

Concomitant chemoradiation has demonstrated an 8% absolute survival advantage in the meta-analysis conducted by Pignon *et al*, and has now become the standard of care in LA SCCHN cancers (10). The combination of induction chemotherapy with concomitant CRT for the treatment of SCCHN has been examined in several clinical trials. Browman *et al* reported a pooled analysis of 18 randomized controlled trials (RCTs) in 3,192 patients, in which concomitant chemotherapy-radiation therapy was compared to radiation therapy alone. Overall, the chemotherapy-radiation therapy arm was superior for the reduction in mortality compared with radiation therapy alone (P<0.0001). The results further demonstrated that platinum-based concomitant CRT is superior to conventional radiotherapy alone in improving survival in locally advanced SCCHN (15).

The current randomized prospective study compared the combination of induction chemotherapy with the TPF regimen followed by concurrent CRT vs. CRT alone in 52 patients with advanced SCCHN at the Regional Cancer Centre in India. The study demonstrated a higher local control at primary and nodal sites with TPF + CRT as compared with CRT alone, though the difference was not statistically significant. The ORR was reported in 82.6% patients with TPF + CRT vs. 72% with CRT.

The TAX323 (12) trial in patients with advanced SCCHN (stages III and IV) with an unresectable disease demonstrated an ORR of 68% with TPF + CRT regimen. The TAX 324 (13) trial reported loco-regional control in 72% patients with both resectable and unresectable advanced SCCHN (stage III or IV) who were treated with 3-cycles of induction chemotherapy with TPF regimen (docetaxel, cisplatin and 5-FU) followed by concomitant radiotherapy. The phase III EORTC trial of TPF followed by radiotherapy in unresectable LA SCCHN (n=177) patients showed a response rate of 67.8% (16). The GSTTC trial that compared the induction TPF followed by concomitant treatment (n=206) vs. concomitant treatment alone (208) in patients with LA SCCHN revealed an ORR of 76% with induction regimen; the CRs were significantly higher in the induction chemotherapy arm (42.5% vs. 28%, P=0.0028) (17). The efficacy results of these studies are comparable to those reported in the present study.

The efficacy of TPF + CRT (n=50) vs. CRT alone (n=51) in patients with LA SCCHN was evaluated by Paccagnella *et al* in a European population (18). CR was reported in 50% patients in the TPF + CRT arm vs. 21.2% in the CRT arm, compared to 78.3 and 64%, respectively as observed in the present study. On subset analysis, a trend for a better response was observed with TPF + CRT vs. CRT across the larynx, oropharynx and hypopharynx in the present study, although the results were not statistically significant.

In the present study, confluent fibrinous mucositis with pain (grade 3 acute mucositis) and grade 4 mucositis was observed

Table II. Subgroup evaluation for both groups.

	TPF + CRT (n=23)		CRT (n=25)		
Parameter	CR (%)	No CR (%)	CR (%)	No CR (%)	P-value
Sex					
Male	18 (85.7)	3 (14.3)	16 (66.7)	8 (33.3)	0.177
Female	1 (50)	1 (50)	0	1 (100)	0.999
Smoker	15 (75)	5 (25)	16 (64)	9 (36)	0.059
Alcohol consumption, n (%)	13 (81.25)	3 (18.8)	15 (68.1)	7 (31.8)	0.469
No alcohol consumption, n (%)	5 (71.4)	2 (28.6)	2 (66.7)	1 (33.3)	0.999
Smoking and alcohol consumption, n (%)	12 (80)	3 (20)	15 (68.2)	7 (31.8)	0.481
Non-vegetarian, n (%)	18 (90)	2 (10)	14 (63.6)	8 (36.4)	0.071
Vegetarian, n (%)	2 (66.7)	1 (33.3)	2 (66.7)	1 (33.3)	0.999
Site					
Oropharynx	11 (78.6)	3 (21.4)	8 (61.5)	5 (38.5)	0.420
Larynx	4 (80)	1 (20)	3 (50)	3 (50)	0.546
Hypopharynx	2 (66.7)	1 (33.3)	3 (50)	3 (33.3)	0.999
Cancer stage					
IVA	13 (72.2)	5 (27.8)	13 (65)	7 (35)	0.633
IVB	4 (80)	1 (20)	3 (60)	2 (40)	0.999

TPF + CRT, induction chemotherapy [TPF (docetaxel and cisplatin, day 1; fluorouracil by continuous infusion, days 1 to 5)] plus radiotherapy; CRT, concomitant chemoradiotherapy alone; CR, complete response.

Table III. Toxicity profile at first follow-up.

Parameter	TPF + CRT (n=23) (%)	CRT (n=25) (%)	P-value
Skin toxicities			
No toxicity	20 (87)	20 (80)	0.612
Mucositis			
No toxicity	19 (82.6)	18 (78.3)	0.458
Grade 1	1 (4.34)	2 (8)	0.999
Salivary Gland Toxicity			
No toxicity	4 (17.4)	11 (44)	0.069
Grade 1	15 (65.2)	9 (36)	0.054
Grade 2	1 (4.3)	0	0.999
Late Toxicity: Depigmentation	16 (69.6)	14 (56)	0.376
Late Toxicity: Subcutaneous Fibrosis	3 (13.0)	3 (12)	0.999
Late Toxicity: Salivary gland			
No toxicity	3 (13.0)	3 (12)	0.999
Grade 1	19 (82.6)	21 (84)	0.999
Grade 2	1 (4.34)	1 (4)	0.999

TPF + CRT, induction chemotherapy [TPF (docetaxel and cisplatin, day 1; fluorouracil by continuous infusion, days 1 to 5)] plus radiotherapy; CRT, concomitant chemoradiotherapy alone.

more often in the TPF + CRT arm (52%) as compared with the CRT arm (18.5%) during radiation treatment (P=0.016). Febrile neutropenia was reported in 1 patient with TPF + CRT. In the DeCIDE trial, the most common grade 3/4 toxicities during induction chemotherapy (TPF + CRT arm) were febrile neutropenia (11%) and mucositis (9%) (19). In the present study, a higher trend for skin, laryngeal and GI toxicities was observed with TPF + CRT compared with CRT. Furthermore, a higher

trend for acute toxicities was observed with the TPF + CRT regimen with significant differences observed for mucositis and hematological toxicities. Grade 3/4 hematological toxicity was markedly higher with TPF + CRT. The acute toxicity results in the present study were comparable to those observed in the DeCIDE, PRADIGM and GSTCC trials (17,19,20). None of the patients in the present study exhibited any skin reactions at the first follow-up and all previous skin reactions were healed completely. However, 1 patient in the TPF + CRT arm and 2 patients in the CRT arm had mucositis and were still healing even after 6 weeks of completion of radiation therapy at the first follow-up; however, at the second follow-up up, all acute toxicities in patients of both the arms were completely healed. A similar trend for higher late toxicities in the form of subcutaneous fibrosis was observed in the TPF + CRT arm as compared with the CRT arm, although the difference in late toxicities was not statistically significant.

Some limitations of the present study should be mentioned. These include the small sample size and the unavailability of the progression-free survival (PFS) and overall survival (OS) data.

In conclusion, local and nodal response at first follow-up was higher with TPF + CRT regimen compared with CRT, although the difference was not statistically significant. The toxicities were higher in the TPF + CRT arm with significant differences for mucositis and hematological toxicities. However, at the first follow-up, mucositis was present in only 1 patient in the TPF + CRT arm vs. 2 patients in the CRT arm. Although in the present study, no statistically significant differences were observed in late toxicities, a longer follow-up time is required to draw any meaningful conclusion. The present study demonstrates the feasibility of sequential therapy in the management of locally advanced head and neck cancer in the Indian population. Triple drug-based sequential therapy was tolerable in the Indian population context. Further large scale studies with longer follow-up times are warranted to confirm these results in Indian patients and in other populations.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

AR and PR performed the research, were involved in the acquisition of data, critically revised the manuscript for important intellectual content, and approved the final manuscript. AR, PR, ManojG, RS and ManishG designed the study, were involved in the data interpretation, critically revised the manuscript for important intellectual content, and approved the final manuscript. All authors made substantial contributions to the present study, read and approved the final manuscript and agree to be accountable for all aspects of the work.

Ethics approval and consent to participate

The present study was conducted after due approval from the Institutional Ethics Committee, Indira Gandhi Government Medical College (IGMC), Shimla, Himachal Pradesh, India. All the patients provided written informed consent for participation.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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