ASIAN JOURNAL OF PHARMACEUTICAL AND CLINICAL RESEARCH

INNOVARE ACADEMIC SCIENCES
Knowledge to Innovation

Vol 18, Issue 3, 2025

Online - 2455-3891
Print - 0974-2441

Research Article

TWO CYCLES OF TPF AS INDUCTION CHEMOTHERAPY IN LOCALLY ADVANCED HEAD-AND-NECK SQUAMOUS CELL CANCER FOR INDIAN PATIENTS: CAN LESS BE MORE?

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Received: 10 January 2025, Revised and Accepted: 22 February 2025

ABSTRACT

Objective: India has a high prevalence of locally advanced head-and-neck (H&N) cancer, with poor outcomes from concurrent chemoradiotherapy (CRT). Many centers widely practice induction chemotherapy (IC) to address this. The commonly used IC regimen with three cycles of docetaxel, cisplatin, and 5-fluorouracil (TPF) often results in poor tolerance and low compliance among Indian patients. This single arm study assess the efficacy, toxicity, and compliance of two cycles of TPF as IC followed by CRT in locally advanced H&N cancers.

Methods: We enrolled adult patients with previously untreated, non-metastatic, newly diagnosed, unresectable, and locally advanced H&N cancer planned for definitive CRT in tumor board. Patients were scheduled for IC with two cycles of TPF followed by concurrent CRT with weekly cisplatin.

Results: Between October 2022 and March 2024, we enrolled a total of 58 patients for the study. After two cycles of IC, 11 patients defaulted, and three had progressive disease. Out of the 44 patients who started CRT, 32 completed the treatment. Three patients were lost to follow-up. We observed a complete response in 27 patients (84.3%). Only two patients had residual disease, and no distant failures occurred. The treatment was well tolerated, with no cases of neutropenia. We noted grade 2 neutropenia in one patient during IC and 11 patients during CRT. Grade 3 mucositis appeared in 5 patients (15.6%) and Grade 3 dysphagia in 7 patients (21.9%).

Conclusion: Two cycles of TPF IC demonstrate good tolerance and efficacy, making them a viable option for sequential treatment of locally advanced H&N cancers in Indian settings.

Keywords: TPF, Induction chemotherapy, Head-and-neck cancer.

 DOI: http://dx.doi.org/10.22159/ajpcr.2025v18i3.53921. Journal homepage: https://innovareacademics.in/journals/index.php/ajpcr

INTRODUCTION

In India, head-and-neck (H&N) malignancies rank among the most prevalent cancers [1]. Unfortunately, nearly 75–80% of these patients are diagnosed at an advanced disease stage. Locally advanced H&N cancer often results in lower cure rates and dismal survival rates despite aggressive treatment. The primary objective in the management of these locally advanced H&N cancer is achieving loco-regional control. Concurrent chemoradiotherapy (CRT), the standard of care for fit patients, has shown limited success. Researchers have explored various treatment intensification approaches to improve outcomes for locally advanced H&N cancer patients, including hypofractionation [2] and induction chemotherapy (IC) [3].

To improve outcomes, various IC regimens have been studied. Phase III clinical trials using three-drug combination chemotherapy regimens that include docetaxel (a taxane drug), cisplatin (a platin drug) and 5-Fluorouracil (TPF) have shown remarkable results [4,5]. A positive response to IC can predict a patient's likelihood of responding well to subsequent CRT. The immediate period after IC remains critical for enhancing treatment outcomes. However, studies have raised concerns about IC compliance and toxicities, which often lead to delays in subsequent standard CRT.

Indian patients with H&N cancer generally show lower tolerance to IC compared to other populations, primarily due to factors such as nutritional deficiencies, advanced disease presentation at diagnosis, and limited access to supportive care [6]. These factors lead to higher rates of treatment-related side effects such as mucositis, neutropenia, and gastrointestinal complications when undergoing TPF IC regimens [7]. Indian H&N cancer patients are also less likely to complete a prescribed therapeutic regimen [8]. Poor compliance significantly increases the risk of persistent neck disease [9]. Therefore, ensuring patient compliance throughout the treatment remains crucial.

Several studies have evaluated alternative IC options for Indian patients, including weekly TPF [10], TPF with oral metronomic therapy [11], cisplatin plus paclitaxel [12], and cisplatin plus ifosfamide [13]. However, the optimal regimen has not yet been definitively established. A modified Indian TPF (docetaxel 75 mg/m^2, cisplatin 75 mg/m^2, and fluorouracil 750 mg/m^{2}on days 1–3) has proven to be the least toxic schedule without compromising subsequent CRT [14]. Patients in limited-resource settings have tolerated the two cycle TPF regimen well, demonstrating excellent response rates. This study aims to assess the efficacy, toxicity, and compliance of sequential therapy, consisting of two cycles of three-drug TPF regimen (docetaxel, cisplatin, and 5-flourouracil) followed by CRT, for locally advanced H&N cancer in Indian patients.

METHODS

Study design

We conducted this study in a tertiary cancer center in western Rajasthan, India. This study was registered as a thesis project for postgraduate course in radiation oncology. We recruited 58 patients with histopathologically confirmed H&N squamous cell carcinoma stage III-IVA. All patients were between 18 and 70 years of age. We included patients with an ECOG performance status of 0–2. We recruited patients over an 18-month period from October 2022 to March 2024 after receiving approval from the Institutional Ethics Committee and

obtaining individual informed consent. Exclusion criteria included: (1) tumors of nasal cavity, nasopharynx, and paranasal sinuses; (2) uncontrolled hepatic and renal dysfunction; (3) a history of previous radiotherapy to the H&N region; or (4) chemotherapy for any other malignancy.

Pre-chemotherapy work-up

We performed complete blood count, liver and renal function tests before every cycle of IC and before every cycle of concurrent chemotherapy. We performed contrast-enhanced computed tomography (CT) [15] scans (or positron emission tomography/CT if feasible) before starting treatment, after completing IC, and 3 months post-treatment. We also performed 2D echocardiography and pure-tone audiometry before chemotherapy. We provided enteral feeding through nasogastric tube and administered IV fluids whenever necessary during the treatment.

IC

After pre-treatment work up, we planned for two cycles of IC using a 3-weekly TPF regimen (Docetaxel 75 mg/m^2 day 1, cisplatin 75 mg/m^2 on day 1, 5-FU 750 mg/m^2 on days 1–3) with granulocyte-colony stimulating factor (G-CSF) support. Three weeks after the second chemotherapy cycle, we conducted a CT scan to assess the loco-regional response using the Response Evaluation Criteria in Solid Tumors (RECIST 1.1).

Chemoradiation

We took all patients, except those with progressive disease, for radiation planning. We immobilized each patient in the supine position with a tailored head-shoulder 4-clamp thermoplastic mask and performed CT simulation on a GE Optima CT simulator. An expert radiation oncologist contoured the target volumes and avoidance structures following the RTOG contouring guidelines. An expert medical physicist performed treatment planning using the Monte-Carlo Optimizer on Monaco v5.11, and the expert radiation oncologist evaluated volumetric modulated arc therapy plans through dose-volume histograms analysis.

We delivered radiation 5 days/week over 7 weeks using conventional fractionation (total dose: 66–70 Gy). Patients received treatment on a VersaHD Linear Accelerator with 6 MV photons. We allowed radiation treatment interruptions only when toxicity affected patient safety or quality of life. If an undue treatment break exceeded 7 days, the physicist planned gap correction. Concurrent chemotherapy consisted of weekly cisplatin 40 mg/m^2.

Assessment and statistics

We reviewed all patients for toxicities at the completion of each cycle of IC, weekly during radiation therapy, and at 1 and 3 months after completing treatment. We assessed disease response at 3 months using the RECIST criteria. An expert statistician performed statistical analysis using the Statistical Package for the Social Sciences software version 26.

RESULTS

We enrolled a total of 58 patients for the study. The median age of the patients was 49 years. Moderately differentiated squamous cell carcinoma (62%) was the most common histological type of tumor. The most common disease site was the oral cavity (47%) followed by oropharyngeal tumors (28%). Most patients (86%) presented with classified as primary stage T_3 or T_4, while the rest had bulky nodal mass (Table 1). We planned all patients for two cycles IC; however, three patients defaulted after the first cycle, and another eight defaulted after completing two cycles.

Out of the remaining 47 patients, 3three patients had progressive disease and were deemed unfit for chemoradiation. The remaining 44 patients included 24 with a partial response and 20 with stable disease. We planned these patients for chemoradiation as per the study protocol. Twelve patients defaulted during chemoradiation, and 32 completed the treatment without undue breaks. Three patients were lost to follow-up, resulting in 29 patients who completed the entire treatment regimen and the planned 3-month follow-up.

Most patients tolerated the induction regimen well. Three patients (5.2%) experienced grade 2 nausea, and no patients reported grade 3 or 4 nausea. Two patients (6.3%) had chemotherapy-induced grade 3 diarrhea. We observed three cases of grade 1 and one case of grade 2 febrile neutropenia. Four patients (6.9%) developed chemotherapy-induced grade 2 anemia and no patients experienced chemotherapy-induced thrombocytopenia (Table 2).

During radiotherapy, patients did not experience severe or life-threatening toxicities. Approximately 15.6% of patients (n=5) developed grade 3 mucositis, necessitating short breaks in radiation for a couple of days and intervention with steroids and mouthwash. This incidence of stomatitis was comparable to rates reported in the TAX studies, (4.6–8.5%). In addition, 7 patients (21.9%) developed grade 3 pharyngitis, leading to dysphagia and requiring intravenous fluids and nasogastric tube feeding.

Most patients received at least four cycles of the planned weekly cisplatin chemotherapy regimen. However, this treatment schedule was associated with significant toxicity, particularly nausea, neutropenia, and anemia. Eleven patients (34.4%) suffered from grade 2 neutropenia during CRT, compared to just one patient (3.1%) during IC. We managed neutropenia during weekly concurrent chemotherapy cycles with subcutaneous injections of G-CSF (300 mcg). After normalizing white blood cell levels, we administered subsequenta chemotherapy cycles without further delay. No grade 3 or 4 neutropenia was observed.

Seven patients (21.9%) experienced grade 2 anemia during CRT compared to four patients (12.5%) during IC ($p<0.001$), requiring transfusions of packed red blood cells. No patients experienced grade 3 or 4 anemia. Three patients (9.4%) reported grade 3 nausea during CRT, while none experienced grade 3 nausea during IC. We ensured adequate hydration through proactive measures such as nasogastric tube placement and IV fluids administration.

After CRT, 5 patients (11.36%) developed grade 2 xerostomia. We prescribed artificial saliva to manage symptoms and improve their quality of life. This study demonstrated a notable overall response rate (ORR) of 65.5% after the two-cycle induction phase of TPF. Among the 29 patients who completed entire treatment course, the overall complete response reached 93.1% (n=27), indicating a high proportion of patients (93.1%) achieving complete remission (Table 3).

DISCUSSION

Overall, 57.5% of global H&N cancers (excluding esophageal cancers) occur in Asia, particularly in India, for both sexes [16]. India reports over 200,000 new cases of H&N cancers annually. Managing these cancers in India presents unique challenges compared to Western countries. A major issue lies in the high rate of loss to follow-up, which complicates conducting clinical trials and accurately reporting their results. More than 80% of cases in both sexes present with regional disease spread at the time of diagnosis. Treatment outcomes in India are approximately 20% poorer than those observed in more developed countries, primarily due to late diagnosis and inappropriate treatment. Mortality from H&N cancers in India accounts for at least half of the incidence, largely because patients often present at advanced stages (Stage III = 39%, Stage IV = 23%).

IC has proven useful for organ preservation, particularly in laryngeal cancers. When administered before local therapies such as radiotherapy or surgery, IC has the potential to decrease the risk of distant metastasis and achieve rapid tumor size reduction, facilitating further local treatment in form of surgery or radiotherapy. Phase III clinical trials using three-drug combination chemotherapy regimens (TPF) have demonstrated remarkable results, with response rates exceeding 90% and complete responses observed in more than 50% of cases [4,5]. The three-drug combination regimen has significantly improved several important clinical outcomes, including higher progression-free

Table 1: Patient characteristics

Characteristics	(n=58)
Gender (%)	
Male	53 (91.4)
Female	5 (8.6)
Median age (in years)	49 (range 24–69)
Histological diagnosis (%)	
WDSCC	13 (22.4)
MDSCC	36 (62)
PDSCC	9 (15.5)
Stage TNM (%)	
T3/4	50 (86.2)
N2a/b	10 (17.2)
N2c	45 (77.5)
N3	2 (3.5)
Primary site	
Oropharynx	16 (28)
Hypopharynx	6 (10)
Larynx	9 (15)
Oral cavity	27 (47)

WDSCC: Well-differentiated squamous cell carcinoma, MDSCC: Moderately differentiated squamous cell carcinoma, PDSCC: Poorly differentiated squamous cell carcinoma

Table 2: Toxicity

Toxicity	Frequency (%)
During IC (n=58)	
Grade 2 nausea	3 (5)
Grade 3 diarrhea	2 (3.5)
Grade 1 neutropenia	3 (5)
Grade 2 neutropenia	2 (3.5)
Grade 2 anemia	4 (7)
During CRT (n=32)	
Grade 2 dermatitis	9 (28)
Grade 2 mucositis	17 (53.1)
Grade 3 mucositis	5 (15.6)
Grade 2 pharyngitis	16 (50)
Grade 3 pharyngitis	7 (21.8)
Grade 2 laryngitis	7 (21.8)
Grade 3 laryngitis	2 (6.3)
Grade 2 neutropenia	11 (34.3)
Grade 2 anemia	7 (21.8)
Grade 2 nausea	14 (43.6)
Grade 3 nausea	3 (9.3)
After CRT (n=29)	
Grade 2 xerostomia	5 (17.9)

IC: Induction chemotherapy, CRT: Chemoradiotherapy

Table 3: Patient compliance and response evaluation

Parameter	Number/Total (%)
Received first cycle IC	58/58 (100)
Received second cycle IC	55/58 (94.8)
Response evaluation after IC (n = 47)	47/55
Progressive disease	8/47 (17)
Stable disease	20/47 (42.5)
Partial response	24/47 (51)
Started CRT	44/58 (75.9)
Received complete CRT	32/44 (72.7)
Lost to follow-up	3/32 (9.3)
Complete response to protocol	27/32 (84.3)

IC: Induction chemotherapy, CRT: Chemoradiotherapy

survival, enhanced overall survival, improved quality of life, and reduced treatment-related side effects.

The use of IC comes with certain inevitable trade-offs. Concerns and controversies exist about the acute toxicity of IC. Severe toxicities can hinder the delivery of subsequent standard CRT, significantly compromising overall treatment compliance [17]. In the Phase II CONDOR study, four cycles of European TPF followed by CRT with high-dose cisplatin (100 mg/m^2 every 21 days) led to the premature termination of the study due to safety concerns. Only 22% (6/27) of patients completed the planned dose of cisplatin during CRT after four cycles of TPF [18]. In the TREMPLIN study, which investigated TPF followed by CRT with concurrent cisplatin versus cetuximab for larynx preservation, only 47% of patients received the planned three cycles of TPF, and just 42% completed full treatment in the cisplatin 3-weekly arm [19]. The TAX 323 trial [4] revealed that after four cycles of TPF IC and radiation alone, 61 of 181 patients did not receive protocol-defined radiotherapy, including 17 patients (10%) who did not receive any radiation [8]. In TAX 324 trial [5], 21% of patients in the TPF induction arm did not receive the prescribed carboplatin-based CRT. Delays and breaks during CRT severely impair loco-regional tumor control.

Several different TPF IC combinations and schedules have been studied. A modified Indian TPF regimen reported in 2004 by Ghi *et al*. in a Phase II feasibility study (docetaxel 75 mg/m^2, cisplatin 75 mg/m^2, and fluorouracil 750 mg/m^2/day on days 1–3) given in two cycles proved to be the least toxic schedule without compromising subsequent CRT [19]. This study found no statistically significant difference in CRT delay, dose delivery, or interruptions longer than 3 days between the IC followed by CRT arm and the CRT-alone arm. Despite differences in TPF doses and regimens, the ORR in the Ghi *et al*. study was reported at 76%, similar to the ORRs seen in the TPF study arms of the TAX 324 and TAX 323 trials, both at 72%.

The optimal IC regimen for the Indian population has not yet been definitively established. Indian patients with H&N cancer generally show lower tolerance to IC compared to other populations, primarily due to factors like nutritional deficiencies, advanced disease presentation at diagnosis and limited access to supportive care. These factors lead to higher rates of treatment-related side effects such as mucositis, neutropenia, and gastrointestinal complications when undergoing TPF IC regimens (cisplatin, fluorouracil, and docetaxel). Malnutrition, prevalent in many Indian populations, further impairs the body's ability to withstand chemotherapy toxicities. The most frequently reported side effects of IC in Indian H&N cancer patients include severe mucositis, neutropenia, nausea and vomiting, fatigue, and dysphagia.

To improve tolerance, clinicians may consider reducing the chemotherapy drug doses based on individual patient factors, providing aggressive nutritional support, managing hydration and pain effectively, closely monitoring blood counts, and promptly addressing clinical symptoms. Concurrent chemotherapy offers only marginal benefits over radiotherapy alone [20]. For concurrent chemotherapy, substituting carboplatin for cisplatin can be justified, as cisplatin displays a superior direct antitumor effect in SCCHN and is equivalent to carboplatin as a radiosensitizer [21]. Regardless of cisplatin/RT delivery schedule, whether weekly or every 3 weeks, a cumulative dose of at least 200 mg/m^2 of cisplatin as monotherapy during CRT is essential for optimal antitumor activity [22].

This study population showed a significant male predominance, as men are more likely to smoke cigarettes, beedi, and use smokeless tobacco products like pan and khaini. In the present study, compliance to IC was around 81%, comparable to other trials in the available literature. The most probable reasons for discontinuing treatment was transient relief from presenting symptoms and poor tolerance to chemotherapy. Maintaining good nutritional status and providing continuous counseling to caregivers throughout the course of therapy could help to improve compliance.

Economic factors also play a critical role, particularly in populations with poor socioeconomic status, where the prolonged treatment process imposes a significant financial burden on caregivers. Often, the

male breadwinner is hospitalized repeatedly during treatment, leading to a substantial increase in the family's financial strain. This situation may prompt patients to default on treatment, highlighting the need for comprehensive patient counseling and support. In the present study, 75% of patients proceeded to receive CRT, a rate comparable to TAX-323 (75%) and TAX-324 (79%). Only 3 (6.4%) patients experienced disease progression after induction phase, suggesting a favorable treatment response.

The addition of docetaxel to the induction regimen significantly increases the treatment's toxicity profile. However, clinicians can manage this toxicity effectively with proper monitoring of blood parameters and prompt interventions. No chemotherapy-related deaths were reported in this study. The incidence of febrile neutropenia was comparable to the Tax 323 and Tax 324 trials. In contrast with the TAX studies, no grade 3 or 4 neutropenia were observed in this study. Notably, the TAX studies did not permit primary prophylaxis with G-CSF, which likely contributed to the high incidence of grade 3 and 4 neutropenia. In this study, we used primary prophylaxis with G-CSF as part of the treatment protocol.

None of the patients experienced any adverse allergic reactions to docetaxel. All patients received steroids as pre-medication to minimize the risk of potential allergic reactions. The induction regimen included the highly emetogenic drug cisplatin. Compared to the TAX trials (5%), this study reported no cases of grade 3 or 4 nausea. We managed nausea effectively through the administration of antiemetic medications such as ondansetron, metoclopramide, and dexamethasone as pre-chemotherapy prophylaxis.

The overall complete response rate at the end of the entire treatment schedule in this study was 84.3% (n=27), which is comparable to the results of the TAX 323 study. These findings suggest that the treatment regimen used in this study effectively achieves a complete response in patients who complete the planned regimen. Longer follow-up of the study population is needed to assess the impact on recurrence-free survival and overall survival rates. Overall, the use of two cycles of TPF as IC followed by concurrent chemoradiation represents a promising approach for the treatment of locally advanced H&N cancers in Indian settings.

CONCLUSION

Sequential IC with two cycles of docetaxel, cisplatin, and 5-fluorouracil followed by concurrent chemoradiation has proven to be effective and well-tolerated in locally advanced H&N cancers, especially in Indian settings. For better results, this regimen requires a careful patient selection while ensuring patient compliance. Further comparative studies are needed.

AUTHORS' CONTRIBUTIONS

Data collection – Dr Anvita Bhati, Dr Shashank Kothari. Contribution to manuscript – Dr Ajay Kumar Yadav, Dr Ramesh Purohit. Writing and revising the manuscript – Dr Anvita Bhati, Dr Ajay Kumar Yadav. Review of the manuscript – Dr Ramesh Purohit, Dr Shashank Kothari. All authors read and approved the final manuscript.

CONFLICTS OF INTEREST

The author declares no conflicts of interest.

AUTHOR FUNDING

The authors received no external funding.

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