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Original Research Article

Bridging therapy during delayed definitive radiotherapy in locally advanced head and neck squamous cell carcinoma: a prospective randomized study comparing induction TPF chemotherapy with oral metronomic chemotherapy

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ABSTRACT

Background: Prolonged waiting periods before definitive radiotherapy remain a major challenge in the management of locally advanced head and neck squamous cell carcinoma (LA-HNSCC), particularly in resource-constrained healthcare settings. Bridging systemic therapy during this interval may help maintain disease control until definitive radiotherapy can be initiated. The aim of the study was to compare the efficacy and safety of induction docetaxel, cisplatin, and 5-fluorouracil (TPF) chemotherapy with oral metronomic chemotherapy (OMCT) as bridging treatment in patients with LA-HNSCC experiencing unavoidable delays before definitive radiotherapy.
Methods: A prospective randomized study was conducted in the Department of Radiotherapy, IPGME&R and SSKM Hospital, Kolkata, India, between February 2020 and November 2022. Sixty patients with biopsy-proven stage III-IVB LA-HNSCC were randomized to receive either two cycles of induction TPF chemotherapy (Arm A) or oral metronomic chemotherapy comprising weekly methotrexate and twice-daily celecoxib (Arm B) while awaiting definitive radiotherapy. Tumour response, treatment-related toxicities, disease-free survival (DFS), overall survival (OS), and quality of life were assessed. Survival outcomes were estimated using the Kaplan-Meier method.
Results: Baseline demographic and clinicopathological characteristics were comparable between the two treatment groups. Induction TPF chemotherapy achieved significantly higher objective tumour response before radiotherapy and superior complete response rates following treatment compared with OMCT. Disease-free survival was significantly longer in the TPF arm, whereas overall survival was comparable between the two groups during the study period.
Conclusions: Induction TPF chemotherapy provided superior tumour response and disease-free survival compared with oral metronomic chemotherapy.

Keywords: Bridging therapy, Head and neck squamous cell carcinoma, Induction chemotherapy, Oral metronomic chemotherapy

INTRODUCTION

Head and neck squamous cell carcinoma (HNSCC) is the seventh most common malignancy worldwide and continues to represent a major public health challenge, particularly in low- and middle-income countries.[1] India bears a disproportionately high burden of HNSCC, accounting for nearly one-third of the global incidence, largely because of the widespread use of tobacco, areca nut, alcohol, and poor oral hygiene. Oral cavity,

oropharyngeal, hypopharyngeal, and laryngeal cancers constitute the majority of these malignancies and are frequently diagnosed at a locally advanced stage.[2,3]

Definitive concurrent chemoradiotherapy (CCRT) remains the standard of care for patients with unresectable locally advanced HNSCC, while surgery followed by appropriate adjuvant therapy is recommended for selected resectable tumours. The addition of concurrent cisplatin to radiotherapy has consistently demonstrated improvements in locoregional control and overall survival compared with radiotherapy alone.[3-5]

Timely initiation of definitive treatment is an important determinant of oncological outcome. Several studies have shown that prolonged waiting time before radiotherapy is associated with accelerated tumour repopulation, increased locoregional failure, and inferior survival. In many high-volume government oncology centres in developing countries, unavoidable delays in initiating radiotherapy remain a major challenge because of limited treatment infrastructure and increasing patient load. Consequently, maintaining disease control during this waiting period has become an important clinical objective.[6,7]

Induction chemotherapy has been explored as a strategy to reduce tumour burden before definitive local treatment. The TAX 323 and TAX 324 trials demonstrated that docetaxel-based induction chemotherapy (TPF: docetaxel, cisplatin, and 5-fluorouracil) achieved higher response rates and improved progression-free survival compared with the conventional PF regimen in patients with locally advanced HNSCC. Although induction chemotherapy has not become a universal standard before concurrent chemoradiotherapy, these studies established TPF as the most active induction regimen in appropriately selected patients.[8,9]

Oral metronomic chemotherapy (OMCT), consisting of continuous low-dose oral molecules having anti-cancer and anti-inflammatory properties, administered without prolonged treatment-free intervals, has emerged as an attractive alternative for patients in whom intensive chemotherapy may not be feasible. Besides direct cytotoxic effects, metronomic therapy exerts anti-angiogenic and immunomodulatory actions while producing substantially lower toxicity. Indian studies have reported encouraging disease control with oral methotrexate-based metronomic regimens in patients with recurrent, metastatic, and locally advanced HNSCC, particularly in resource-constrained settings.[10-13]

Despite increasing interest in OMCT, prospective randomized data comparing induction TPF chemotherapy with oral metronomic chemotherapy as bridging therapy during unavoidable delays before definitive radiotherapy are scarce. The present study was therefore undertaken to compare the efficacy and safety of induction TPF chemotherapy and oral metronomic chemotherapy as bridging treatment in patients with locally advanced HNSCC awaiting definitive concurrent chemoradiotherapy.

Aim and objectives

Primary objective of the study was to assess the treatment response, 1 year DFS and 1 year OS in two arms.

Secondary objectives were to assess the toxicity profile and quality of life in the two arms.

METHODS

Study design and setting

This prospective, randomized, comparative study was conducted in the department of radiotherapy at IPGME&R and SSKM Hospital, West Bengal, India, after obtaining approval from the institutional ethics committee. The study was carried out between February 2020 and November 2022. Written informed consent was obtained from all participants before enrolment.

Study population

Patients aged 18-70 years with histologically confirmed, previously untreated, locally advanced squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, or larynx were screened.

Eligible patients had stage III-IVB disease (AJCC 8th edition), an eastern cooperative oncology group (ECOG) performance status of 0-2, and were planned for definitive concurrent chemoradiotherapy but experienced unavoidable delays before initiation of radiotherapy.[14]

Patients with distant metastasis, prior chemotherapy or radiotherapy, second primary malignancy, pregnancy, severe uncontrolled comorbid illness, or contraindications to chemotherapy were excluded.

Randomization

Seventy eligible patients were randomized in a 1:1 ratio into two treatment arms using computer-generated random numbers.

Arm A

Induction TPF chemotherapy, 2 cycles 21 days apart followed by definitive concurrent chemoradiotherapy.

Arm B

Oral metronomic chemotherapy (OMCT) continuously till the commencement of definitive concurrent chemoradiotherapy.

Initially, thirty-five patients were analysed in each arm. In ARM A, 2 patients didn't receive intervention and 3 were lost to follow up. While in ARM B, 5 patients were lost to follow up, hence total effective participants in each arm were 30 (Figure 1).

Treatment protocol

Patients in Arm A received induction TPF chemotherapy consisting of docetaxel (75 mg/m^2), cisplatin (75 mg/m^2), and 5-fluorouracil (750 mg/m^2) according to the institutional protocol before definitive treatment.

Patients in Arm B received oral metronomic chemotherapy comprising low-dose oral methotrexate 10mg twice weekly and celecoxib 200 mg daily, five days a week, during the waiting period before radiotherapy, as per institutional protocol.

Following completion of bridging therapy, all patients underwent definitive external beam radiotherapy with concurrent weekly cisplatin according to institutional standards.

Response assessment

Baseline clinical examination and contrast-enhanced computed tomography (CECT) of the head and neck were performed before initiation of bridging therapy.

Tumour response was assessed after completion of bridging therapy, six weeks after chemoradiotherapy, and subsequently during follow-up using response evaluation criteria in solid tumours (RECIST) version 1.1.[15]

Responses were classified as: complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD).

Toxicity assessment

Treatment-related adverse events were evaluated weekly during treatment and at each follow-up visit using the common terminology criteria for adverse events (CTCAE), version 5.0.[16] Both acute and late toxicities were documented and graded.

Quality of life assessment

Quality of life (QoL) was assessed at baseline and during follow-up using the European organisation for research and treatment of cancer quality of life questionnaire core-30 (EORTC QLQ-C30) and the head and neck cancer module (EORTC QLQ-H&N35).[17,18]

Follow-up

Patients were evaluated six weeks after completion of chemoradiotherapy, every three months during the first year, and every six months thereafter. Clinical examination and imaging were performed whenever clinically indicated.

Disease-free survival (DFS) was defined as the interval from randomization to the first documented recurrence, disease progression, or death from any cause.

Overall survival (OS) was calculated from the date of randomization to death from any cause or the last follow-up.

The median follow-up duration was 26 months (range: 16-30 months).

Statistical analysis

Data were analysed using IBM statistical package for the social sciences (SPSS) statistics version 24 (IBM Corp., Armonk, NY, USA).

Categorical variables were expressed as frequency and percentage and compared using the Chi-square test or Fisher's exact test, as appropriate.

Continuous variables were expressed as mean ± standard deviation and compared using the independent samples t-test.

Disease-free survival and overall survival were estimated using the Kaplan-Meier method, and differences between treatment groups were analysed using the log-rank test.

A two-sided p value <0.05 was considered statistically significant.

RESULTS

Patient characteristics

Between February 2020 and November 2021, 70 eligible patients were randomized. Ten patients were excluded from the final analysis because of treatment discontinuation or loss to follow-up. The remaining 60 patients completed the planned treatment and were analysed, with 30 patients each in the induction TPF chemotherapy (Arm A) and oral metronomic chemotherapy (Arm B) groups (Figure 1).

The baseline demographic and clinicopathological characteristics of the study population are summarized in Table 1. The mean age was 54.23±8.64 years in the TPF arm and 55.40±9.12 years in the OMCT arm (p=0.23). The majority of patients were male in both groups. Oropharynx was the most common primary tumour site, followed by the larynx and hypopharynx. Most patients presented with stage IVA disease and had an ECOG performance status of 1. There were no statistically significant differences between the two treatment groups with respect to age, sex, primary tumour site, stage, nodal status, or ECOG

performance status, indicating comparable baseline characteristics.

Clinical response following bridging therapy

Patients receiving induction TPF chemotherapy demonstrated a significantly higher objective response rate compared with those receiving oral metronomic chemotherapy. Partial response was observed more frequently in the TPF arm, whereas stable disease predominated in the OMCT arm. Progressive disease was uncommon in both treatment groups. The difference in response distribution between the two arms was statistically significant ($p<0.001$).

Treatment response after completion of definitive therapy

Treatment response assessed six weeks after completion of definitive chemoradiotherapy is presented in Table 2. Complete response was achieved more frequently among patients treated with induction TPF chemotherapy than among those who received oral metronomic chemotherapy. Although partial response and residual disease were observed in both groups, the overall treatment response favoured the TPF arm. The difference was statistically significant.

Disease status at six months

At six months after completion of treatment, a higher proportion of patients in the TPF arm remained disease free compared with the OMCT arm (Table 2). Locoregional recurrence occurred more frequently among patients receiving oral metronomic chemotherapy, while distant metastases were infrequent in both groups. The difference in disease status between the two treatment arms was statistically significant.

Acute treatment-related toxicity

Treatment-related toxicities are summarized in Table 3. Patients receiving induction TPF chemotherapy experienced a higher incidence of grade 3-4 haematological and gastrointestinal toxicities compared with those treated with OMCT. Oral metronomic chemotherapy was generally well tolerated, with most adverse events limited to grade 1-2 mucositis, nausea, and fatigue. No treatment-related mortality was observed in either treatment arm.

Survival analysis

During a median follow-up of 26 months (range: 16-30 months), disease-free survival was significantly better in patients receiving induction TPF chemotherapy.

The estimated 1-year disease-free survival was higher in Arm A than in Arm B (Figure 2). Kaplan-Meier analysis demonstrated a statistically significant difference between the two treatment groups (log-rank $p<0.05$). As the data got matured, we calculated the 2 year DFS. The estimated 2 year DFS was not statistically significant in both the arms (long rank $p=0.56$) (Table 4, Figure 4). Mean DFS was comparable in both arms, and median DFS has not achieved in either arm. The 1-year overall survival was comparable and not statistically significant in either arm.

Table 1: Baseline demographic and clinicopathological characteristics.

Variables	TPF (Arm A) n=30, N (%)	OMCT (Arm B) n=30, N (%)	P value
Mean age (years)	54.23	55.40	0.23
Primary site			
Oral cavity	2 (6.7)	2 (6.7)	0.41
Hypopharynx	7 (23.3)	9 (30.0)	
Larynx	8 (26.7)	12 (40.0)	
Oropharynx	13 (43.3)	7 (23.3)	
ECOG performance status			
0	7 (23.3)	11 (36.7)	0.50
1	19 (63.3)	15 (50.0)	
2	4 (13.3)	4 (13.3)	
AJCC stage			
III	1 (3.3)	1 (3.3)	0.66
IVA	27 (90.0)	28 (93.3)	
IVB	2 (6.7)	1 (3.3)	

Table 2: Treatment response during follow-up.

Responses	6 weeks TPF n (%)	6 weeks OMCT n (%)	6 months TPF n (%)	6 months OMCT n (%)	12 months TPF n (%)	12 months OMCT n (%)
Complete Response	21 (70.0)	11 (36.7)	21 (70.0)	11 (36.7)	21 (70.0)	15 (50.0)
Partial Response	4 (13.3)	5 (16.7)	4 (13.3)	5 (16.7)	2 (6.7)	1 (3.33)
Stable Disease	4 (13.3)	3 (10.0)	2 (6.7)	3 (10.0)	4 (13.3)	1 (3.33)
Progressive Disease	1 (3.3)	11 (36.7)	3 (10.0)	11 (36.7)	3 (10.0)	13 (43.3)
Overall p-value	<0.001		0.04		<0.05	

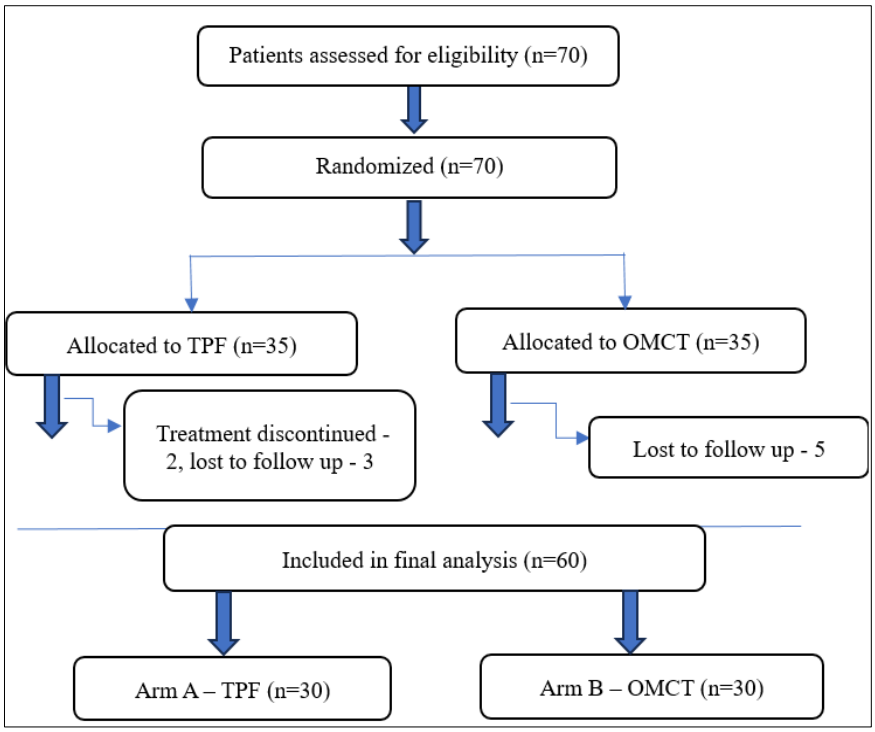

Figure 1: Consort flow diagram.

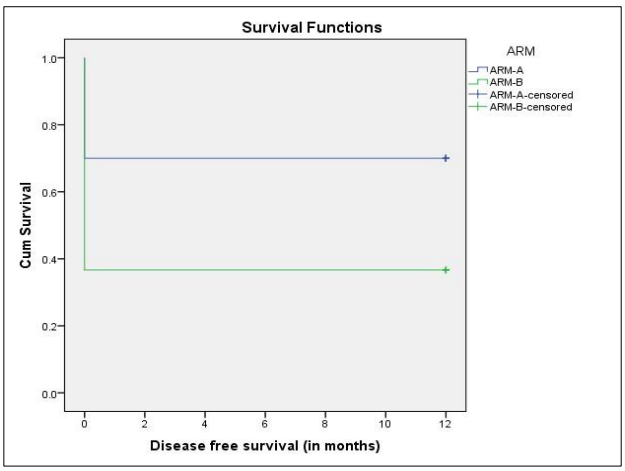

Figure 2: 1-year DFS between two arms.

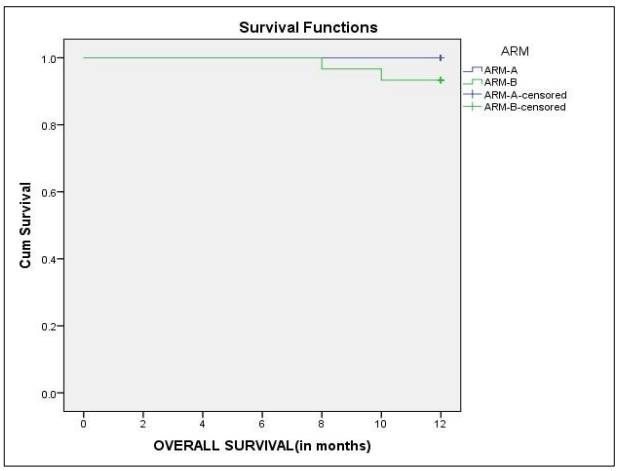

Figure 3: 1-year overall survival curve between two arms.

Table 3: Treatment-related toxicities.

Toxicity	Grade	TPF (n=30), N (%)	OMCT (n=30), N (%)	P value
Acute toxicities (during treatment)				
Anaemia	I	19 (63.3)	24 (80.0)	
	II	09 (30.0)	03 (10.0)	
	III	02 (6.7)	03 (10.0)	0.15
Febrile neutropenia	I	17 (56.7)	22 (73.3)	
	II	02 (6.7)	05 (16.7)	
	III	11 (36.7)	03 (10.0)	0.03
Mucositis	I	09 (30.0)	13 (43.3)	
	II	11 (36.7)	15 (50.0)	
	III	10 (33.3)	02 (6.7)	<0.01

Continued.

Toxicity	Grade	TPF (n=30), N (%)	OMCT (n=30), N (%)	P value
Late toxicities (3 months after radiotherapy)				
Mucositis	I	16 (53.3)	13 (43.3)	
	II	09 (30.0)	15 (50.0)	
	III	05 (16.7)	02 (6.7)	0.21
Anaemia	I	21 (70.0)	27 (90.0)	
	II	06 (20.0)	03 (10.0)	
	III	03 (10.0)	0	0.04

Table 4: Disease-free survival and quality of life.

Variable	TPF (Arm A)	OMCT (Arm B)	P value
Median follow-up (months)	26	26	-
Average delay before RT (days)	43.5± 6.84	48.33± 8.49	0.28
1-year disease-free survival	70.0%	50.0%	<0.05
2-years disease free survival	66.70%	53.30 %	0.58
1-year overall survival	90.00%	86.67%	0.73
Pretreatment QoL Score	49.40	51.73	0.56
QoL at 6 months	48.50	59.43	<0.05
QoL at 12 months	48.70	61.86	<0.05

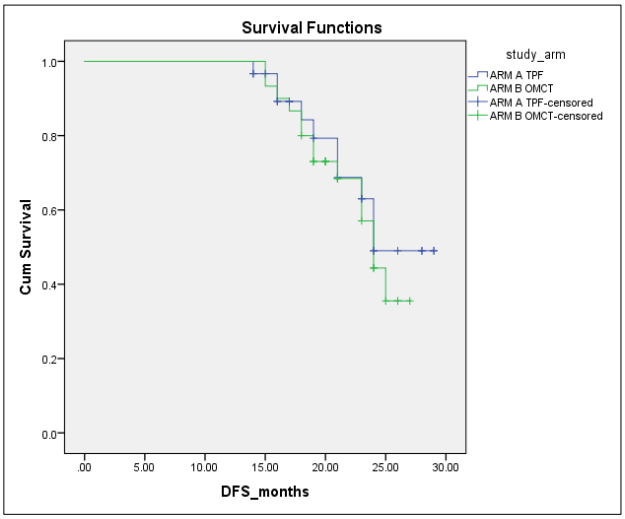

Figure 4: 2-year disease free survival curve.

DISCUSSION

The present prospective randomized study compared induction TPF chemotherapy with OMCT as bridging treatment during unavoidable delays before definitive concurrent chemoradiotherapy in patients with locally advanced head and neck squamous cell carcinoma (LA-HNSCC). The study demonstrated that induction TPF chemotherapy achieved significantly higher objective tumour response rates and superior disease-free survival compared with OMCT. However, OMCT was associated with substantially lower treatment-related toxicity and provided acceptable disease control, suggesting that it may serve as a practical alternative when intensive chemotherapy is unsuitable or resources are limited.

Timely initiation of definitive treatment is a critical determinant of oncological outcomes in HNSCC. Prolonged waiting times before radiotherapy have consistently been associated with accelerated tumour repopulation, poorer locoregional control, and reduced survival. These observations provide the biological rationale for administering active systemic therapy during unavoidable treatment delays rather than observation alone.[19,20]

In the present study, induction TPF chemotherapy produced a significantly higher tumour response before radiotherapy than OMCT. These findings are consistent with the landmark TAX 323 and TAX 324 trials, which established docetaxel-based induction chemotherapy as the most effective induction regimen for patients with locally advanced HNSCC. Both trials demonstrated improved tumour response and progression-free survival with TPF compared with the conventional PF regimen. Although these studies evaluated induction chemotherapy before definitive treatment rather than as bridging therapy, the superior cytoreductive effect of TPF observed in our study is biologically plausible and aligns with their findings.[8,9]

Oral metronomic chemotherapy, despite producing lower objective response rates, demonstrated encouraging disease stabilization with a favourable safety profile. Continuous administration of low-dose chemotherapy is believed to inhibit tumour angiogenesis, modulate the tumour microenvironment, and reduce the development of resistant tumour clones while minimizing systemic toxicity. These mechanisms may explain the ability of OMCT to maintain disease control during prolonged waiting periods before definitive treatment.[21,22]

Our findings closely parallel those reported by Shenoy et al who evaluated oral metronomic chemotherapy as preoperative therapy in patients with advanced resectable oral cavity squamous cell carcinoma awaiting surgery. They observed meaningful clinical benefit with low rates of disease progression and minimal severe toxicity, allowing most patients to proceed to definitive treatment without significant deterioration. Although their study involved surgery rather than radiotherapy, both studies

support the concept that metronomic chemotherapy represents an effective bridging strategy when delays in definitive treatment are unavoidable.[13]

Indian investigators have also reported favourable outcomes with metronomic chemotherapy in recurrent, metastatic, and locally advanced HNSCC. Patil et al demonstrated that low-dose oral methotrexate-based metronomic therapy provided durable disease control with acceptable toxicity in patients unsuitable for intensive systemic therapy. Similar findings have been reported by Pai et al highlighting the affordability, outpatient feasibility, and improved treatment compliance associated with OMCT, particularly in resource-limited healthcare settings.[23,24]

Although 1year disease-free survival was significantly superior in the TPF arm, no statistically significant difference in overall survival was observed between the treatment groups during the available follow-up period. This finding may be explained by the relatively small sample size, the median follow-up of 26 months, and the influence of salvage therapies administered after disease recurrence. Larger multicentric studies with longer follow-up are required to determine whether the improved tumour response achieved with induction TPF ultimately translates into an overall survival advantage.

Treatment-related toxicity remains an important consideration when selecting an appropriate bridging strategy. As expected, induction TPF chemotherapy was associated with a higher incidence of Grade III hematological toxicity, particularly febrile neutropenia, and mucositis whereas OMCT was generally well tolerated. The favourable toxicity profile of OMCT may be particularly relevant for elderly patients, those with borderline performance status, and individuals with nutritional compromise who may not tolerate intensive induction chemotherapy. The quality-of-life score analysis also showed better results with OMCT.

There is subsequent delay in diagnosis and treatment initiation in Indian Healthcare System, more delay results in upstaging and poor prognosis of disease.[25] OMCT helps in bridging the treatment initiation gap.

The present study has several strengths. It is one of the few prospective randomized studies directly comparing induction TPF chemotherapy with OMCT as bridging treatment before delayed definitive radiotherapy. Nevertheless, certain limitations should be acknowledged. This was a single-centre study with a relatively small sample size, limiting the generalizability of the findings. The follow-up period was insufficient to evaluate long-term survival outcomes comprehensively. In addition, molecular biomarkers such as HPV status and p16 expression were not evaluated, which may have influenced treatment response in selected patients.

CONCLUSION

Induction TPF chemotherapy demonstrated superior tumour response and significantly improved disease-free survival compared with oral metronomic chemotherapy when used as bridging treatment during unavoidable delays before definitive concurrent chemoradiotherapy in patients with locally advanced head and neck squamous cell carcinoma. However, oral metronomic chemotherapy was associated with substantially lower treatment-related toxicity, good treatment compliance, and satisfactory disease control, making it a practical and cost-effective alternative for carefully selected patients who are unsuitable for intensive chemotherapy or are managed in resource-constrained settings. While induction TPF should remain the preferred bridging strategy for fit patients, oral metronomic chemotherapy represents a feasible option when treatment delays are unavoidable. Larger multicentre randomized studies with longer follow-up are warranted to validate these findings and define the optimal bridging approach in this clinical setting.

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