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Comparing long-term efficacy and safety of GP versus TPF sequential chemoradiotherapy for locoregionally advanced nasopharyngeal carcinoma: a propensity score-matched analysis

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Abstract

Purpose To evaluate the long-term efficacy and safety of GP and TPF sequential chemotherapy regimens in patients with locoregionally advanced nasopharyngeal carcinoma (LA-NPC).

Methods From 2005 to 2016, a total of 408 LA-NPC patients treated with GP or TPF sequential chemoradiotherapy were retrospectively included. Propensity Score Matching (PSM) was employed to balance the baseline variables. Survival outcomes and acute toxicities were compared between both groups.

Results A total of 230 patients were selected by 1:1 PSM. At a median follow-up of 91 months, no significant differences were observed between the matched GP and TPF groups regarding 5-year overall survival, progression-free survival, distant metastasis-free survival, and locoregionally relapse-free survival (83.4% vs. 83.4%, $P=0.796$; 75.6% vs. 68.6%, $P=0.301$; 86.7% vs. 81.1%, $P=0.096$; and 87.4% vs. 87.2%, $P=0.721$). Notable disparities in adverse effects were identified, with higher incidences of grade 3/4 thrombocytopenia in the GP group while grade 3/4 leukopenia and neutropenia in the TPF group. Though not recorded in our cohort, combined with the FAERS database, thrombotic adverse reactions are a concern for the GP regimen, while the TPF regimen requires vigilance for life-threatening adverse reactions such as septic shock, acute respiratory distress syndrome, and laryngeal edema.

Conclusion No significant difference in long-term outcomes was observed between the GP and TPF sequential chemotherapy regimens for LA-NPC. Differences in adverse effects should be noted when choosing the regimen.

Keywords Nasopharyngeal carcinoma, Sequential chemotherapy, IMRT, Survival, FAERS

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Introduction

Nasopharyngeal carcinoma (NPC) exhibits endemic in Southern China, Southeast Asia, and North Africa [1–4]. Despite the long-term survival for early-stage NPC patients, nearly 80% patients are diagnosed at late stages due to the insidious symptoms [5, 6]. With the widespread application of Intensity-Modulated Radiation Therapy (IMRT), local control has been greatly improved in patients with locoregionally advanced NPC (LA-NPC) [7]. However, distant metastasis remains the primary cause of treatment failure [8]. Therefore, current research on treating LA-NPC primarily focuses on systemic chemotherapy.

Systemic chemotherapy is essential for improving overall survival and reducing the risk of distant metastasis in LA-NPC [9–11]. Consequently, the integration of systemic chemotherapy with radiotherapy has emerged as the standard treatment approach for LA-NPC. Presently, the commonly prescribed systemic chemotherapy regimens include GP (gemcitabine plus cisplatin) and TPF (docetaxel, cisplatin, and fluorouracil), each having shown effectiveness in clinical trials [10, 12]. Thus, the best choice of systemic chemotherapy regimen remains debate.

This study performs a retrospective analysis on the long-term prognosis and safety profile of LA-NPC patients treated with combined IMRT and either GP or TPF sequential chemotherapy. Additionally, this research screens adverse reactions associated with both GP and TPF regimens reported in the FAERS database. This study aims to provide improved guidance for future clinical decision-making.

Methods

Patients

We included patients diagnosed with LA-NPC at Fudan University Shanghai Cancer Center between September 2005 and December 2016. Staging was performed according to the AJCC 8th edition. Initial evaluations included physical exams, laboratory tests, nasopharyngoscopy, enhanced magnetic resonance imaging (MRI) of the nasopharynx and enhanced MRI/computed tomography (CT) of cervical regions. Positron emission and computer tomography (PET/CT) or a combination of chest CT scans, abdominal ultrasound/CT scans, and ECT bone scans were used to exclude metastasis. Oral examinations were conducted prior to radiotherapy to address any dental issues, with extractions performed when necessary. Inclusion criteria were: (1) pathologically confirmed NPC; (2) stage III-IVA; (3) received GP or TPF sequential chemotherapy; (4) received IMRT. Exclusion criteria included: (1) distant metastasis; (2) prior history of cancer. This study was approved by the hospital's ethics committee, and informed consent was obtained from all patients before treatment.

Treatment

All patients in this study received sequential chemotherapy combined with IMRT. The chemotherapy regimens included the GP regimen (gemcitabine 1,000 mg/m^2 on days 1 and 8, cisplatin 25 mg/m^2 on days 1–3, q3w) and the TPF regimen (docetaxel 60 mg/m^2 on day 1, cisplatin 25 mg/m^2 on days 1–3, fluorouracil 500 mg/m^2 per day, continuously infused over 120 h, q3w).

Patients received two cycles of induction chemotherapy (IC), then followed by IMRT and two cycles of adjuvant chemotherapy (AC) using the same regimen, unless the patient refused or showed intolerance or progressive disease. If acute myelosuppression or organ dysfunction occurred, chemotherapy was delayed. Up to a 2-week delay of chemotherapy was allowed, or the chemotherapy will be terminated. A 20% reduction in the dose for the next cycle was applied in the event of grade 4 hematological or ≥Grade 3 non-hematological toxicities. Modifications up to 2 times are allowed, or chemotherapy will be terminated. IMRT should begin within 21–28 days from the first day of the last induction chemotherapy cycle [13], the target volume delineation and dose prescription were as with previously published studies [14]. AC was administrated 4 weeks after completing radiotherapy, up to a 2-week delay of AC was allowed, or the AC will be terminated.

Following up

After completing all treatments, patients were followed up every three months during the first two years, every six months from the third to the fifth year, and annually thereafter. Follow-up assessments included physical examinations, nasopharyngoscopy, hematologic tests, and imaging evaluations. The primary endpoints of this study were overall survival (OS) and progression-free survival (PFS). OS was defined as the time from treatment initiation to the patient's death or last follow-up, while PFS was defined as the time from treatment initiation to the occurrence of recurrence/distant metastasis/death or last follow-up. Secondary endpoints included distant metastasis-free survival (DMFS) and locoregional relapse-free survival (LRFS). DMFS was defined as the time from treatment start to the detection of distant metastasis, and LRFS was defined as the time from treatment start to the detection of locoregional relapse. Weight loss was defined as the percentage difference between post-treatment and pre-treatment weight relative to pre-treatment weight.

FAERS database

The FAERS database, developed by the Food and Drug Administration (FDA), is an open-access database for spontaneously reporting adverse drug reactions. Data can be obtained from the official website: https://fis.fda.gov/extensions/FPD-QDE-FAERS/FPD-QDE-FAERS.html. The Medx_UIMA_1.3.8 software is used for standardizing drug names, and adverse reactions are categorized using MedDRA 26.1.

Statistical analysis

In the baseline data section, chi-square tests or Fisher's exact tests were employed. Patient matching between the GP and TPF groups was conducted using Propensity Score Matching (PSM) at a 1:1 ratio. Survival rates were calculated using the Kaplan-Meier (KM) method, and differences between groups were assessed using the log-rank test. Multivariate analysis was performed using Cox regression. Statistical analyses were carried out in SPSS, while graphs were generated using Prism 8. A two-tailed *P*-value of less than 0.05 was considered statistically significant. Data from the FAERS database were processed using R software, which included removing duplicate reports based on case ID and report date, extracting major adverse drug reactions related to medications, and applying signal detection methods such as ROR, PRR, and BCPNN.

Results

Patients

The baseline characteristics of 408 patients with LA-NPC were shown in Table 1. Statistical differences were noted between both groups in terms of gender and the number of chemotherapy cycles. We employed PSM based on patient age, gender, KPS score, pathological type, T stage, N stage, clinical stage, and the number of chemotherapy cycles to match the two groups. After matching, as shown in Table 1, there were no statistical differences in baseline data between both groups.

Survivals

For the entire cohort, the median follow-up duration was 91 months (ranging from 38 to 177 months). The patterns of treatment failure for both groups are displayed in Table 2. No differences were observed in nasopharyngeal recurrence, retropharyngeal recurrence, cervical recurrence, or distant metastasis between both groups either in the original cohort or in the matched cohort.

Table 1 Characteristics of the original and PSM cohorts

Characteristics	No. of patients (%)	Original cohort		*P*	Propensity-score matched cohort		*P*
		GP group (*n* = 122) (%)	TPF group (*n* = 286) (%)		GP group (*n* = 115) (%)	TPF group (*n* = 115) (%)	
Age				0.017			0.792
<48y	204 (50.0)	50 (41.0)	154 (53.8)		50 (43.5)	52 (45.2)	
≥48y	204 (50.0)	72 (59.0)	132 (46.2)		65 (56.5)	63 (54.8)	
Gender				0.447			0.875
Male	311 (76.2)	96 (78.7)	215 (75.2)		89 (77.4)	90 (78.3)	
Female	97 (23.8)	26 (21.3)	71 (24.8)		26 (22.6)	25 (21.7)	
KPS score				0.781			0.114
<90	193 (47.3)	59 (48.4)	134 (46.9)		53 (46.1)	65 (56.5)	
≥90	215 (52.7)	63 (51.6)	152 (53.1)		62 (53.9)	50 (43.5)	
Pathologic type				0.586			1.000
WHO I	13 (3.2)	3 (2.5)	10 (3.5)		3 (2.6)	3 (2.6)	
WHO II/III	395 (96.8)	119 (97.5)	276 (96.5)		112 (97.4)	112 (97.4)	
T stage				0.520			0.138
T1-2	141 (34.6)	45 (36.9)	96 (33.6)		39 (33.9)	50 (43.5)	
T3-4	267 (65.4)	77 (63.1)	190 (66.4)		76 (66.1)	65 (56.5)	
N stage				0.174			0.768
N0-1	126 (30.9)	32 (26.2)	94 (32.9)		32 (27.8)	30 (26.1)	
N2-3	282 (69.1)	90 (73.8)	192 (67.1)		83 (72.2)	85 (73.9)	
Clinical stage				0.057			0.693
III	198 (48.5)	68 (55.7)	130 (45.5)		61 (53.0)	64 (55.7)	
IVa	210 (51.5)	54 (44.3)	156 (54.5)		54 (47.0)	51 (44.3)	
Chemotherapy cycles				< 0.001			0.755
1–2	68 (16.7)	11 (9.0)	57 (19.9)		11 (9.6)	10 (8.7)	
3	85 (20.8)	12 (9.8)	73 (25.5)		12 (10.4)	17 (14.8)	
4	255 (62.5)	99 (81.1)	156 (54.5)		92 (80.0)	88 (76.5)	

KPS score, Karnofsky performance status score

Table 2 Treatment failure patterns of LA-NPC patients in the GP and TPF groups

Failure pattern	Original cohort		*P*	Propensity-score matched cohort		*P*
	GP group (*n* = 122) (%)	TPF group (*n* = 286) (%)		GP group (*n* = 115) (%)	TPF group (*n* = 115) (%)	
Nasopharyngeal recurrence			0.236			0.502
Yes	13 (10.7)	20 (7.0)		13 (11.3)	9 (7.8)	
No	109 (89.3)	266 (93.0)		102 (88.7)	106 (92.2)	
Retropharynx recurrence			0.247			> 0.999
Yes	4 (3.3)	4 (1.4)		3 (2.6)	3 (2.6)	
No	118 (96.7)	282 (98.6)		112 (97.4)	112 (97.4)	
Neck recurrence			0.681			0.823
Yes	10 (8.2)	20 (7.0)		10 (8.7)	12 (10.4)	
No	112 (91.8)	266 (93.0)		105 (91.3)	103 (89.6)	
Distant metastases			0.773			0.176
Yes	19 (15.6)	49 (17.1)		17 (14.8)	26 (22.6)	
No	103 (84.4)	237 (82.9)		98 (85.2)	89 (77.4)	

By the last follow-up, 103 patients had died across the entire cohort (44 in the GP group and 59 in the TPF group), while in the matched cohort, 70 patients had died (40 in the GP group and 30 in the TPF group). As illustrated in Fig. 1, the five-year OS, PFS, DMFS, and LRFS were 84.4%, 75.1%, 85.3%, and 88.6% respectively for the entire cohort, and 83.4%, 72.1%, 83.9%, and 87.3% for the matched cohort. After matching, there were no significant statistical differences in the five-year OS (83.4% vs. 83.4%, $P=0.796$), PFS (75.6% vs. 68.6%, $P=0.301$), DMFS (86.7% vs. 81.1%, $P=0.096$), or LRFS (87.4% vs. 87.2%, $P=0.721$) between the GP and TPF groups.

Recognizing the potential impact of chemotherapy cycles on treatment efficacy, we used PSM to align the GP and TPF groups based on patient demographics and clinical characteristics such as age, gender, KPS score, pathological type, T stage, N stage, and clinical stage. After matching, as shown in Table S3, there were no statistical differences in baseline data across both groups, except in the number of chemotherapy cycles. Furthermore, Fig. S1 illustrated that there were no significant differences in the five-year OS (81.9% vs. 82.0%, $P=0.972$), PFS (74.6% vs. 68.9%, $P=0.185$), DMFS (85.8% vs. 81.5%, $P=0.073$), and LRFS (87.3% vs. 87.0%, $P=0.724$) between the GP and TPF groups in the matched cohort.

Furthermore, we categorized the TPF group into two subgroups based on the number of completed chemotherapy cycles: the TPF-C0 group, which did not complete 4 cycles, and the TPF-C1 group, which did complete 4 cycles. As illustrated in Fig. S2, there were no significant statistical differences in the five-year OS (82.5% vs. 88.3%, $P=0.091$), PFS (73.4% vs. 76.7%, $P=0.410$), DMFS (82.7% vs. 86.9%, $P=0.140$), LRFS (88.3% vs. 89.8%, $P=0.627$) between both groups.

As shown in Table 3, multivariate Cox regression analysis was conducted to calculate potential prognostic confounders, incorporating multiple factors including gender (male vs. female), age (< 48 years vs. ≥ 48 years), KPS (< 90 vs. ≥ 90) T stage (T1-2 vs. T3-4), N stage (N0-1 vs. N2-3), Clinical stage (III vs. IVa), chemotherapy regimen (GP vs. TPF), chemotherapy cycle (1–3 vs. 4), and weight loss (≤ 10% vs. > 10%). The analysis indicated that the GP and TPF chemotherapy regimens were not associated with patient prognosis. However, we found that age was predictive of OS (HR 0.594; 95% CI 0.354–0.996; $P=0.048$), clinical stage was strongly predictive of OS (HR 0.462; 95% CI 0.278–0.769; $P=0.003$) and PFS (HR 0.468; 95% CI 0.297–0.735; $P<0.001$), weight loss (HR 0.408; 95% CI 0.222–0.748; $P=0.004$) and N stage (HR 0.361; 95% CI 0.141–0.927; $P=0.034$) were predictive of DMFS.

Treatment compliance

Acute toxicities during chemoradiotherapy in the original and matched cohorts for patients are depicted in Table 4. Significant differences were observed in the incidence of Grade 3/4 leukopenia, neutropenia, and thrombocytopenia between the GP and TPF groups, with P values less than 0.001 in both cohorts. Although the TPF group experienced more Grade 3/4 mucositis compared to the GP group, this difference was not statistically significant ($P=0.052$ in original cohort and $P=0.059$ in PSM cohort).

These acute toxicities may prevent patients from completing all four cycles of chemotherapy. As detailed in Table 1 and Table S4, approximately half of the patients could not complete all four cycles of TPF. Specifically, 64 (22.4%) patients were unable to complete the regimen due to myelosuppression. An additional 2 (0.7%) patients discontinued treatment due to disease progression, while 29 (10.1%) patients chose to stop treatment. The remaining 35 (12.2%) patients could not finish due to various reasons, including herpes zoster, renal dysfunction, liver dysfunction, diarrhea, facial neuritis, periodontitis, and common colds.

Furthermore, several factors related to chemotherapy side effects may influence efficacy. As shown in Table S5, there were no significant statistical differences in time to

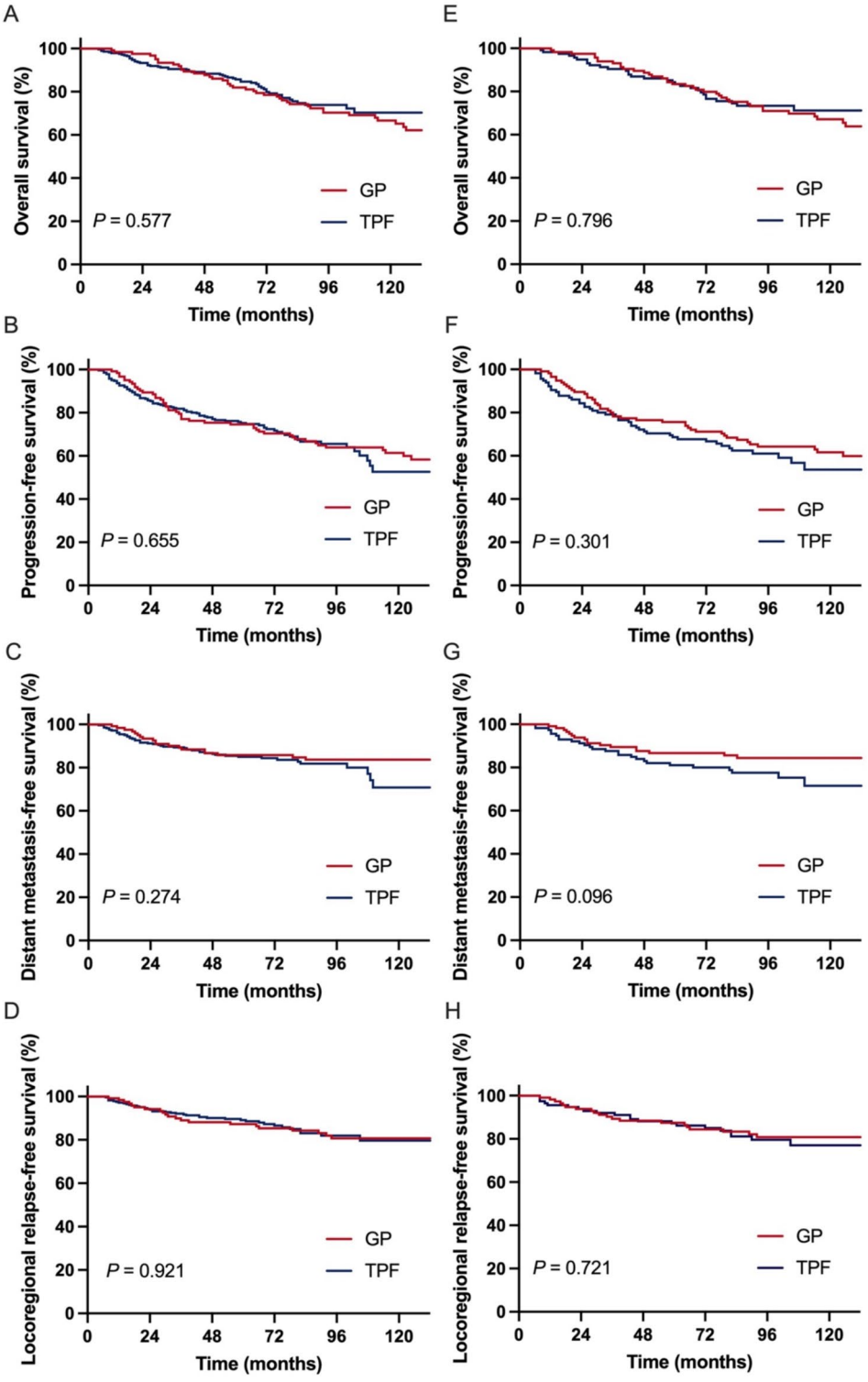

Fig. 1 Kaplan-Meier analysis of survival curves for the two treatment groups. **A**/**B**/**C**/**D**: original cohorts, **E**/**F**/**G**/**H**: PSM cohorts

Table 3 Cox multivariate regression analysis of potential prognostic factors for OS, PFS, DMFS and LRFS rates in PSM cohort

Variable	Hazard ratio	95%CI	*P*
OS			
Chemotherapy regimen: GP vs. TPF	1.074	0.653–1.765	0.778
Age: <48y vs. ≥ 48y	0.594	0.354–0.996	0.048
Clinical stage: III vs. IVa	0.462	0.278–0.769	0.003
PFS			
Chemotherapy regimen: GP vs. TPF	0.739	0.479–1.141	0.172
Clinical stage: III vs. IVa	0.468	0.297–0.735	< 0.001
DMFS			
Chemotherapy regimen: GP vs. TPF	0.623	0.334–1.162	0.137
N stage: N0-1 vs. N2-3	0.361	0.141–0.927	0.034
Weight loss: ≤10% vs. > 10%	0.408	0.222–0.748	0.004
LRFS			
Chemotherapy regimen: GP vs. TPF	0.889	0.473–1.672	0.716

radiotherapy (TTR) (P=0.397) or radiotherapy interruption (RTI) (P=0.350) between GP and TPF groups [13, 15]. Notably, there was a statistical difference (P=0.048) in the radiotherapy completion rates between both groups. However, given the extremely small proportion of patients who did not complete radiotherapy, and the fact that it was caused by sudden diseases such as cerebral hemorrhage or economic constraints, this finding require validation with a larger sample size.

In the FAERS database, we screened for adverse events (AEs) related to GP and TPF treatments, excluding irrelevant System Organ Classes (SOCs). The top 20 AEs for each chemotherapy regimen are displayed in Table S1. Anemia and thrombocytopenia are the most common AEs associated with the GP regimen, while neutropenia and anemia are the most prevalent AEs for the TPF regimen, which was consistent with the data of our cohort.

Although severe AEs like neutropenic sepsis were rare in our cohort, occurring in only three cases, they require careful consideration and assessment. Therefore, we identified 310 strong signal AEs with an IC025 value of ≥1.0 associated with the GP regimen and 195 with the TPF regimen according to the FAERS database to highlight some of the AEs of interest (Table S2). Both treatments showed strong infection signals within the 'Infections and infestations' category, with septic shock and sepsis occurring more prevalent with TPF. Similarly, peripheral arterial thrombosis rates were higher in the GP regimen, which also uniquely reported arterial thrombosis, ischemic necrosis, extremity necrosis, peripheral ischemia, capillary leak syndrome, and embolism. In the gastrointestinal system, the TPF regimen exhibited stronger signals for neutropenic colitis and enterocolitis, whereas esophageal perforation and gastrointestinal necrosis were specific in the TPF regimen. Both regimens caused cardiac disorders such as arteriospasm coronary, but acute coronary syndrome and acute myocardial infarction were unique in the GP regimen, and cardiotoxicity and ventricular fibrillation were specific in the TPF regimen. In the 'Blood and lymphatic system disorders' category, the GP regimen showed higher rates of hematotoxicity, leukopenia, thrombocytopenia, and anemia, while neutropenia was more frequent with TPF. In 'Hepatobiliary disorders', cholangitis was more common in the GP regimen. In 'Respiratory, thoracic and mediastinal disorders', TPF had a higher incidence of acute respiratory distress syndrome, while pulmonary embolism and laryngeal edema were unique to GP and TPF, respectively. In 'General disorders and administration site conditions', mucosal inflammation was unique to TPF. Neurotoxicity was more frequent in GP in the 'Nervous system disorders' category, and in 'Renal and urinary disorders,' toxic nephropathy was higher in GP.

Discussion

Under the combined use of IMRT and concurrent chemotherapy, patients with LA-NPC achieve good local control [10]. However, distant metastasis remains a significant challenge [16]. Current research primarily focuses on systemic chemotherapy, with the addition of adjuvant or induction chemotherapy potentially helping to manage distant metastasis [12]. Clinical studies indicate that concurrent chemoradiotherapy combined with AC can help control distant metastasis, though it may have poor tolerability [11]. Other studies suggest that IC combined with concurrent chemoradiotherapy can not only improve quality of life but also enhance patient tolerability [17]. However, the adverse reactions during concurrent chemoradiotherapy remain a concern [18]. In this study, we employed sequential chemoradiotherapy (IC+IMRT+AC), and over 80% of patients treated with

Table 4 Grade 3/4 acute toxicities during sequential chemoradiotherapy in the original and PSM cohorts

Toxicities	Original cohort		*P*	Propensity-score matched cohort		*P*
	GP group (*n* = 122) (%)	TPF group (*n* = 286) (%)		GP group (*n* = 115) (%)	TPF group (*n* = 115) (%)	
Leukopenia	7(5.7)	67(23.4)	< 0.001	5(4.3)	25(21.7)	< 0.001
Neutropenia	13(10.7)	122(42.7)	< 0.001	12(10.4)	45(39.1)	< 0.001
Anemia	1(0.8)	0(0.0)	0.125	1(0.9)	0(0.0)	0.316
Thrombocytopenia	14(11.5)	1(0.3)	< 0.001	14(12.2)	1(0.9)	< 0.001
Mucositis	20(16.4)	72(25.2)	0.052	20(17.4)	32(27.8)	0.059

the GP regimen completed the full course of chemotherapy. This suggests that in addition to induction/adjuvant chemotherapy combined with concurrent chemoradiotherapy, sequential chemotherapy alongside radiotherapy is also a viable option worth considering [18–20].

The commonly used systemic chemotherapy regimens include PF, TPF, GP, and TP. Previous research has shown TPF to be superior to PF and TP, although it leads to a higher incidence of grade 3/4 adverse reactions, particularly leukopenia and neutropenia [21–26]. Therefore, it is essential to explore alternative options. Previous multicenter randomized study indicated that GP is more effective than PF in treating recurrent and metastatic nasopharyngeal carcinoma [27]. Additionally, other studies have demonstrated the effectiveness of the GP regimen in locally advanced stages of the disease [28, 29]. Research also suggests that the GP regimen outperforms PF and TP in locally advanced nasopharyngeal carcinoma, with comparable adverse reactions [14, 30, 31]. However, the optimal choice of systemic chemotherapy for patients with locally advanced nasopharyngeal carcinoma remains to be determined in clinical practice. In this study, the efficacy of the GP and TPF regimens was found to be comparable, which aligns with previous reports [32–35].

Recent studies indicate that IC combined with concurrent chemoradiotherapy leads to weight loss in patients with LA-NPC [36–38]. Pre-treatment obesity is a protective prognostic factor for this cancer, and weight loss during treatment is associated with poorer outcomes [39–41]. Multivariate analysis of this study also proved that significant weight loss is an independent prognostic factor for distant metastasis (HR 0.408; 95% CI 0.222–0.748; $P=0.004$). Therefore, it is crucial to monitor patients' weight during treatment and provide timely nutritional support. Considering the high frequency incidence of mucositis in TPF regimen, which was usually thought to influence the food intake, the GP regimen may be more suitable for patients with nutritional risks.

With the advancement of IMRT and systemic chemotherapy, the prognosis for patients with LA-NPC has significantly improved. Consequently, there is increasing focus on the toxic side effects caused by treatment. Our study indicates that the GP regimen results in a lower incidence of grade 3 and 4 acute toxic reactions compared to the TPF regimen, aligning with previous findings [32–35]. From the FAERS database, we observed differences in reported adverse reactions between the GP and TPF regimens. The GP regimen is strongly associated with thrombosis, suggesting the need for monitoring coagulation parameters and performing pulmonary artery CTA and lower limb Doppler ultrasound during treatment. On the other hand, the TPF regimen may cause life-threatening conditions such as septic shock, ARDS, and laryngeal edema. While these adverse reactions are rare and not occurred in our cohort, they are critical and require vigilance during use. Overall, the adverse reactions caused by the GP regimen are generally manageable.

This study has several limitations. First, it is retrospective, inherently subject to selection bias. Second, despite subsequent matching efforts, initial disparities in baseline data existed between patients receiving different chemotherapy regimens. Third, plasma EBV-DNA load is associated with prognosis, but it had not yet been established as standard at our institution in the period of this study (2005–2016). In future follow-ups, we plan to incorporate this data.

Conclusion

In summary, there is no significant difference in long-term prognosis for LA-NPC between the groups receiving GP and TPF sequential chemotherapy regimens. However, there are notable differences in the incidence of adverse reactions between the GP and TPF regimens which should be concerned when choosing the regimens. Further phase III clinical trials are needed for comparison.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12885-024-12932-0.

Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

Supplementary Material 4

Supplementary Material 5

Supplementary Material 6

Supplementary Material 7

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Author contributions

Ying Zhu: materials and methods, data analysis, manuscript preparation, manuscript editing. Fen Xue: conceptualization, data collection, data analysis, manuscript edits and revision.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
This study was approved by the hospital's ethics committee, and informed consent was obtained from all patients before treatment.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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