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Gemcitabine combined with cisplatin *vs.* taxane, cisplatin, and fluorouracil in the treatment of locally advanced nasopharyngeal carcinoma: a retrospective case-control study

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Abstract. – OBJECTIVE: Reports of the efficacy of induction chemotherapy (IC) combined with concurrent chemoradiotherapy (CCRT) on locoregionally advanced nasopharyngeal carcinoma (NPC) are scarce. This study aimed to compare the clinical outcomes of the GP (gemcitabine plus cisplatin) regimen and the TPF (taxane, cisplatin and 5-FU) regimen combined with CCRT in patients with NPC.

PATIENTS AND METHODS: This study retrospectively analyzed 827 patients with advanced NPC who received IC combined with CCRT in People's Hospital of Rizhao, China from January 2006 to June 2012. The propensity score method was used to reduce the effects of the observed confounding between the GP and TPF groups. Study end points were disease-free survival (DFS) and overall survival (OS). In total, 694 patients received GP or TPF as the IC treatment program. Propensity score matching identified 166 patients in each cohort.

RESULTS: The 5-year OS and DFS rates of the entire cohort were 83.5% and 80.9%, respectively. GP was associated with a significantly improved 5 year OS (87.4% *vs.* 79.2%, $p< 0.001$), and DFS (86.2% *vs.* 78.5%, $p< 0.001$) rates compared with the TPF group. In the PSM (propensity score-matching) cohort, the GP group showed a significantly better OS (HR, 1.842, 95% CI:1.627-2.588; $p= 0.011$), and DFS (HR, 1.904, 95% CI: 1.742-2.737; $p= 0.004$) compared with the TPF group in multivariable analyses. The prevalence of acute adverse events of neutropenia and leukopenia were higher in severe (grade 3-4) adverse blood events in the TPF group ($p<0.05$). Thrombocytopenia had more adverse reactions in the GP group ($p<0.05$). The main non-hemotoxicities were nausea and vomiting, while the TPF group was slightly higher ($p=0.031$).

CONCLUSIONS: The clinical efficacy of the GP regimen combined with CCRT for the treatment of locoregionally advanced NPC may be better than that of the TPF regimen.

Key Words:
Nasopharyngeal carcinoma, Induction chemotherapy, Propensity score matching, Gemcitabine.

Introduction

Nasopharyngeal carcinoma (NPC) is a highly malignant head and neck tumor, which is less common in Europe, America, Oceania and Latin America, but is a common malignant tumor in China, with morbidity and mortality of 60.6% and 34.1% per 1000 people, respectively[1]. In the age of 2 d radiation therapy INT0099, this phase III randomized clinical trials confirmed that cisplatin plus radiotherapy of NPC in the same period in progress - free survival (PFS) and overall survival (OS) were superior to radiation alone[2]. However, distant metastasis is still a key problem, with over 30%-40% of patients with locally advanced nasopharyngeal carcinoma having distant metastasis after receiving concurrent chemoradiotherapy[3]. Therefore, more effective treatment programs are needed.

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Compared with adjuvant chemotherapy, induced chemotherapy (IC) is well tolerated by patients, who can early intervene in the micro-metastasis of the tumor, reduce the tumor load, and improve the sensitivity of follow-up radiotherapy. Recent clinical trials have confirmed that the addition of induced chemotherapy on the basis of concurrent radiotherapy and chemotherapy can significantly improve the disease-free survival rate, total productivity, and survival rate without distant metastasis, suggesting that induced chemotherapy may have value in improving the prognosis of patients with locally advanced nasopharyngeal carcinoma[4-6].

Sun et al[4] conducted a randomized controlled clinical study and found that induced chemotherapy with taxane, cisplatin, and fluorouracil (TPF) could significantly improve the survival of patients with locally advanced nasopharyngeal carcinoma. Based on this study, the National Comprehensive Cancer Network (NCCN) guidelines recommend TPF as the preferred induction chemotherapy regimen for nasopharyngeal carcinoma (category 1 recommendation). However, the toxicity of TPF induced chemotherapy regimens from Europe and the United States cannot be ignored. Although in the clinical study of TPF led by Sun et al[4], the dose of the three chemotherapeutic drugs was decreased by 20% compared with the classical TPF regimen in Europe and America, the prevalence of toxic side effects was still high[4]. The prevalence of grade 3 or above neutrophilic granulocytopenia and diarrhea during induced chemotherapy was higher, and the prevalence of grade 4 side effects was 15.1%. In the experimental group, 1 patient died of neutrophilic granulocytopenia and granulocytic infection due to induction chemotherapy. Therefore, it is urgent to seek efficient and low toxicity induction chemotherapy.

Gemcitabine plus cisplatin (GP) is the first-line chemotherapy for recurrent and metastatic nasopharyngeal carcinoma. Zhang et al[7] showed that GP-induced chemotherapy can significantly improve the efficacy, delay disease progression, and reduce the risk of death. In the present study, retrospective propensity score matching analysis was used for patients with advanced nasopharyngeal carcinoma who received GP and TPF induction chemotherapy regimens, and the effects of the two treatment regimens on the clinical effect of patients were compared in more dimensions.

Patients and Methods

Patients

According to the American Joint Commission on the Cancer Staging System, we identified newly diagnosed and pathologically biopsied patients with stage III-IV nasopharyngeal carcinoma who received IC and concurrent chemoradiotherapy (CCRT) initial treatment (using GP or TPF as the IC regimen) in our hospital from January 1, 2006 to June 30, 2012. Patients who were treated with anticancer drugs other than the initial treatment with GP or TPF, who were missing medical data, or who died during treatment from other causes unrelated to this study were excluded.

Additional patient information was collected from the hospital information system and paper medical records, including demographic characteristics, pathological diagnosis, date of diagnosis, imaging results, family history, smoking history, Carden scale score, chemotherapy patterns and drugs, radiation techniques and dosages, and follow-up. All patients' tumors were reclassified according to magnetic resonance imaging (MRI) or computed tomography (CT) imaging in conjunction with the 7th edition of the American Joint Committee on Cancer Classification System. The main outcomes were OS and DFS. All data, including the diagnosis of metastasis and regional recurrence, were reviewed by the first two authors and the last author. Blood and gastrointestinal reactions were classified as acute IC related toxicity and side effects according to the National Cancer Institute Standard for Adverse Events version 4.0. The study obtained the informed consent of each patient. The investigation was approved by the Ethics Committee of People's Hospital of Rizhao, China.

IC Regimen

TPF-treated patients received taxane (60 mg/m^2) or paclitaxel (150 mg/m^2) and cisplatin (60 mg/m^2) as a 4-h intravenous infusion on day 1, followed by fluorouracil (600 mg/m^2) as a 24-h continuous infusion on days 1-5. GP treated patients received gemcitabine at a dose of 1 g/m^2 on days 1 and 8 and cisplatin at a dose of 80 mg/m^2 on day 1, which were intravenously administered once every 3 weeks for three cycles.

CCRT Regimen

RT was given to the nasopharynx and neck using intensity-modulated radiotherapy (IMRT) or two-dimensional radiotherapy (2D-CRT) 5 days/

week. The IMRT dose-volume histograms of the treatment targets and critical normal structures were evaluated. The prescribed dose was 70 Gy to the primary tumor, and 60-66 Gy to any involved cervical lymph nodes in 30-32 fractions. 2D-CRT-accumulated radiation doses were 68-76 Gy, with 2 Gy per fraction applied to the primary tumor, and 60-66 Gy applied to involved cervical lymph nodes. Our policy was to accept a plus or minus 5% variation across the target. All patients received a concurrent chemotherapy regimen of cisplatin weekly or every 3 weeks during radiotherapy.

Follow-Up

The first hospital stay was taken as the starting point of the study, each subsequent hospital stay and follow-up was taken as follow-ups, and the last imaging study, clinical consultation, or telephone follow-up was taken as the end point of the study. The final follow-up was updated on August 17, 2017. The follow-up was conducted every 3 months for the first 2 years after IC+CCRT treatment, followed by reexamination every 6 months for the next 3 years, and then annually. These included a physical exam, chest X-ray, abdominal ultrasound, head and neck MRI or bone scan. All survival data were analyzed for the time between the diagnostic solstice study outcome and the last follow-up.

Statistical Analysis

All statistical analyses were performed using the SAS 9.4 software (SAS Institute, Cary, NC, USA). The χ^2-test was used for categorical variables, and the *t*-test was used for continuous variables. Survival was estimated by the Kaplan-Meier method and compared using the log-rank test. Multivariate Cox proportional hazards regression analysis was used to calculate the hazard ratios (HRs) and 95% confidence intervals (CIs). In all analyses, two-tailed $p<0.05$ was considered statistically significant.

Propensity score analysis is a statistical method that balances pre-existing differences across treatment conditions achieving a similar condition as randomization and thus estimating causal effects in non-randomized experimental designs. The four stages in propensity score analysis are propensity score estimation, equating or balancing procedures, balance checking, and outcome analysis. The propensity score-matched (PSM) analysis was used to adjust for potential biases associated with factors related to receiving specific treatments to balance observed confounders between the GP group and the TPF group[8]. Propensity scores for all patients were calculated using a multiple logistic regression[9] with the following covariates: age, sex, smoking status, pathological T stage, pathological N stage, overall stage, the total dose of cisplatin D, and the number of IC cycles. The PSM analyses were performed using R (version 3.2.6). Statistical significance was set at 0.05, and all tests were two-tailed.

Results

Baseline Data Before and After Being Propensity Matched

From January 2005 to June 2013, 827 patients with locally advanced nasopharyngeal carcinoma received IC+CCRT, of which 694 received GP or TPF as the IC regimen (Figure 1). Of the 694 patients, 463 (66.7%) received GP+CCRT and 231 (33.3%) received TPF +CCRT. Before matching, a larger percentage of patients receiving TPF for IC were smokers ($p<0.001$). After matching, the distribution between the two groups was balanced and no statistical difference was found. The baseline characteristics of the study cohort are shown in Table I. The median follow-up was 58 months (11-106 months).

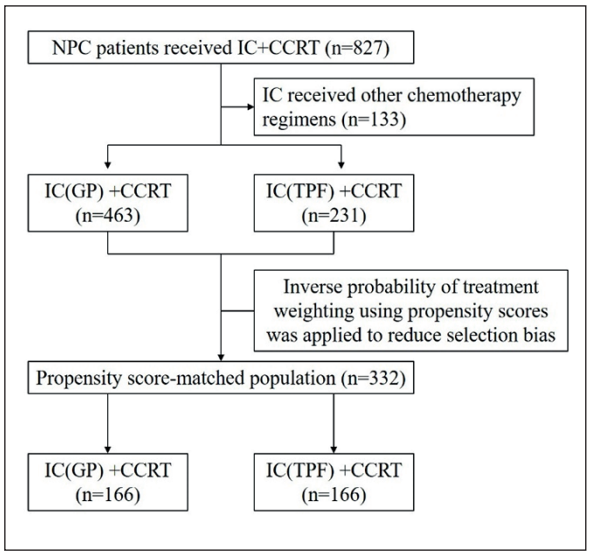

Figure 1. Patients flow diagram. IC, induction chemotherapy; CCRT, concurrent chemoradiotherapy; GPF, gemcitabine and cisplatin; TPF, taxane, cisplatin, and fluorouracil.

Table I. Patients' baseline data before and after propensity score matching.

Variables	Entire cohort			Propensity score-matched cohort		
	GP (n = 463)	TPF (n = 231)	p	GP (n = 166)	TPF (n = 166)	p
Sex			0.465			0.806
Male	335 (72.4)	161 (69.7)		121 (72.9)	119 (71.7)	
Female	128 (27.6)	70 (30.3)		45 (27.1)	47 (28.3)	
Age (years)			0.37			0.581
≤ 50	207 (44.7)	95 (41.1)		76 (45.8)	71 (42.8)	
>50	256 (55.3)	136 (58.9)		90 (54.2)	95 (57.2)	
Smoking status			0.044			0.553
Smokers	162 (35.0)	99 (42.9)		54 (32.5)	49 (29.5)	
Non-smokers	301 (65.0)	132 (57.1)		112 (67.5)	117(70.5)	
T stage			0.241			0.782
T1	21 (4.5)	14 (6.0)		7 (4.2)	6 (3.6)	
T2	46 (9.9)	33 (14.3)		15 (9.0)	14 (8.4)	
T3	229 (49.5)	102 (44.2)		89 (53.6)	82 (49.4)	
T4	167 (36.1)	82 (35.5)		55 (33.1)	64 (38.6)	
N stage			0.356			0.601
N0	37 (8.0)	23 (10.0)		10 (6.0)	13 (7.8)	
N1	139 (30.0)	69 (29.9)		49 (29.5)	48 (28.9)	
N2	191 (41.3)	103 (44.6)		66 (39.8)	73 (44.0)	
N3	96 (20.7)	36 (15.6)		41 (24.7)	32 (19.3)	
Overall stage			0.351			0.359
III	251 (54.2)	112 (48.5)		91 (54.8)	83 (50.0)	
IVa	110 (23.8)	60 (26.0)		42 (25.3)	39 (23.5)	
IVb	102 (22.0)	59 (25.5)		33 (19.9)	44 (26.5)	
Total dose of cisplatin D (mg/m^2)			0.044			0.509
≤ 300	211 (45.6)	124 (53.7)		91 (54.8)	85 (51.2)	
> 300	252 (54.4)	107 (46.3)		75 (45.2)	81 (48.8)	
Number of IC cycles			0.514			0.688
< 3	98 (21.2)	44 (19.0)		37 (22.3)	34 (20.5)	
≥ 3	365 (78.8)	187 (81.0)		129 (77.7)	132 (79.5)	

Survival Outcomes Before and After Being Propensity Matched

The 5-year OS and DFS rates of the entire cohort were 83.5% and 80.9%, respectively and the 5-year OS and DFS rates for the GP group *vs*. TPF group were 87.4% *vs*. 79.2%, respectively ($p< 0.001$, Figure 2a), 86.2% *vs*. 78.5% ($p< 0.001$, Figure 2b). In the PSM cohort, the 5-year OS and DFS rates in the GP and TPF groups were 87.9% *vs*. 83.1% ($p= 0.009$, Figure 2c), 86.7% *vs*. 81.4% ($p< 0.001$, Figure 2d), respectively. The Cox proportional risk model was used for multi-factor analysis. The results confirmed that the GP-based IC regimen significantly improved the 5-year OS rates (HR =1.476; 95% CI: 1.166 1.692; p =0.002), and DFS (HR = 1.502; 95% CI: 1.174 1.772; p = 0.014). The same result was obtained in the PMS cohort, OS (HR = 1.842; 95% CI: 1.627 2.588; p =0.011), and DFS (HR = 1.904; 95% CI: 1.742 2.737; p = 0.004), Table II.

Toxicity and Side Effects

Toxicity and side effects of the PSM cohort showed that neutropenia and leukopenia were higher in severe (grade 3-4) adverse blood events in the TPF group than in the GP group ($p<0.05$). Thrombocytopenia had more adverse reactions in the GP group ($p<0.05$). The main non-hemotoxicities were nausea and vomiting, and in the TPF group they were slightly higher ($p=0.031$). Only a few patients in the two groups had liver damage or acute renal toxicity, as shown in Table III.

Discussion

In this study, we reviewed and analyzed patients receiving IC+CCRT treatment for locally advanced nasopharyngeal carcinoma. The analysis results showed that the GP-based IC regimen

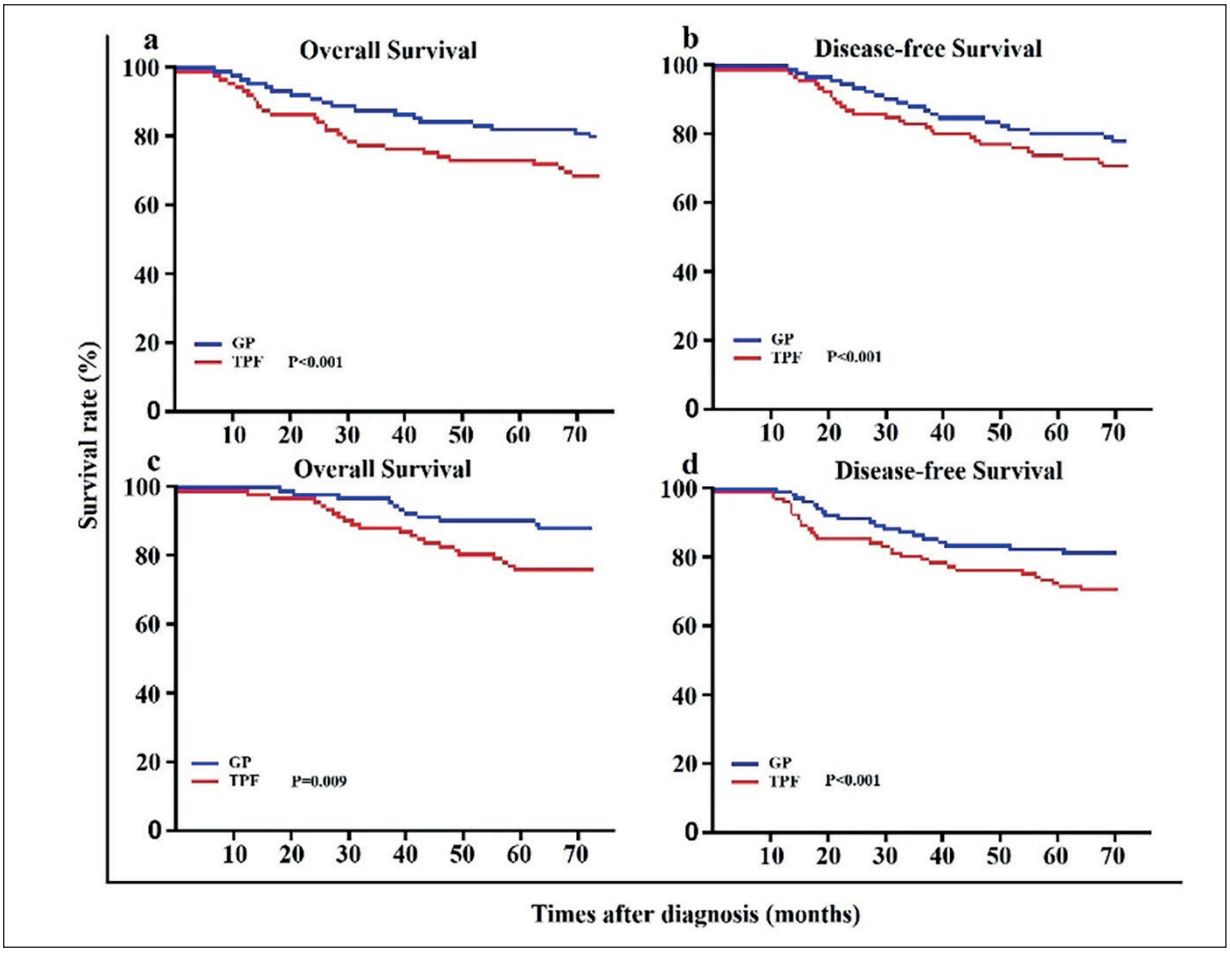

Figure 2. Kaplan-Meier estimates of the survival of the entire cohort and propensity score matched cohort. **a**: Overall survival of the entire cohort; **b**: Disease-free survival of the entire cohort; **c**: Overall survival of the matched propensity score; **d**: Disease-free survival of the matched propensity score.

significantly improved the OS and DFS rates of the patients compared with the TPF regimen, and the side effects were relatively smaller. The analysis using PSM to balance the confounding factors also obtained consistent results.

A recent meta-analysis showed a survival benefit in concurrent chemoradiotherapy combined with adjuvant chemotherapy, but most of the included studies used two-dimensional radiotherapy[10]. A retrospective analysis of 869 patients with rhinitis found that concurrent chemoradiotherapy was not an independent prognostic factor affecting survival, and the study also found that a cumulative cisplatin dose over 300 mg/m^2 was an independent prognostic factor affecting DMFS, DFS, and OS[11]. Therefore, the cumulative dose of cisplatin was included in the clinical feature analysis. Analysis showed that the cumulative dose of cisplatin in the GP regimen group was higher than that in the TPF regimen group in all the investigated cohorts.

The advantages of the extensive application of induced chemotherapy in the clinic mainly lie in the rapid reduction of tumor load, the reduction of clinical symptoms, and the favorable design of the radiotherapy plan to protect normal tissues after tumor retraction. The tumor blood supply was better before radiotherapy, and the effective concentration of chemotherapeutic drugs could be achieved at the tumor site. It can also kill micro – metastatic foci. The patient's tolerance to induced chemotherapy was better than that of concurrent chemotherapy and adjuvant chemotherapy[6,12-14]. II period clinical trials with prompt induction chemotherapy improved the 3-year OS rate (94.1% *vs.* 67.7%, $p = 0.012$)[15]. Peng et al[16] compared 3738

Table II. Summary of the multivariable analyses of prognostic factors before and after propensity score matching.

Variable	Entire cohort				Propensity score-matched cohort			
	OS HR (95% CI)	*p*	DFS HR (95% CI)	*p*	OS HR (95% CI)	*p*	DFS HR (95% CI)	*p*
Gender (male *vs.* female)	0.788 (0.572-1.127)	0.209	0.733 (0.504-1.016)	0.138	0.939 (0.784-1.544)	0.422	1.028 (0.813-1.027)	0.315
Age	1.021 (1.012-1.037)	0.013	1.019 (1.009-1.033)	0.018	1.023 (1.008-1.039)	0.011	1.026 (1.011-1.047)	0.009
Smoking (yes *vs.* no)	1.033 (0.802-1.228)	0.566	1.012 (0.753-1.304)	0.642	1.124 (0.842-1.447)	0.622	1.022 (0.737-1.233)	0.702
T stage (T1-2 *vs.* T3-4)	1.417 (1.182-1.659)	0.006	1.227 (1.079-1.341)	0.011	1.296 (0.983-1.552)	0.173	1.332 (0.877-1.602)	0.226
N stage (N0-1 *vs.* N2-3)	1.322 (1.201-1.508)	0.001	1.202 (1.031-1.355)	0.028	1.288 (0.991-1.626)	0.088	1.306 (0.967-1.532)	0.117
Overall stage (III *vs.* IV)	1.178 (0.861-1.654)	0.302	1.420 (1.219-1.797)	0.019	1.767 (1.538–2.392)	0.001	1.891 (1.663-2.592)	0.001
IC regimen (GP *vs.* TPF)	1.476 (1.166-1.692)	0.002	1.502 (1.174-1.722)	0.014	1.842 (1.627-2.588)	0.011	1.904 (1.742-2.737)	0.004

Table III. Comparison of adverse reactions among the three groups.

Adverse reactions	GP (n = 166)		TPF (n = 166)		p
	Grade 0-2	Grade 3-4	Grade 0-2	Grade 3-4	
Leukopenia	128 (77.1)	38 (22.9)	111 (66.9)	55 (33.1)	0.038
Neutropenia	117 (70.5)	49 (29.5)	98 (59.0)	68 (41.0)	0.029
Anemia	142 (85.5)	24 (14.5)	136 (81.9)	30 (18.1)	0.372
Thrombocytopenia	141 (84.9)	25 (15.1)	153 (92.2)	13 (7.8)	0.039
Febrile neutropenia	166 (100.0)	0 (0)	161 (97.0)	5 (3.0)	0.071
Hepatoxicity	163 (98.2)	3 (1.8)	162 (97.6)	4 (2.4)	1.00
Nephrotoxicity	164 (98.8)	2 (1.2)	163 (98.2)	3 (1.8)	1.00
Nausea and vomiting	125 (75.3)	41 (24.7)	107 (64.5)	59 (35.5)	0.031
Diarrhea	166 (100.0)	0 (0)	164 (98.8)	2 (1.2)	1.00

patients with locally advanced nasopharyngeal carcinoma who received the TPF regimen, the PF regimen, and the TP regimen (taxane combined with cisplatin) for induction chemotherapy, and found that the TPF regimen was superior to the PF regimen in the 3-year DFS rate (84.7% *vs.* 79.3%, p=0.004), the OS rate (93.6% *vs.* 90.8%, p=0.047), and the LRFS rate (94.1% *vs.* 90.4%, p=0.002). However, the application of TPF has certain limitations. Fluorouracil requires a continuous intravenous drip, which easily leads to the risk of venous infection and thrombosis[17]. Taxane requires dexamethasone pretreatment, which may increase the risk of diabetes and gastric ulcer[18]. The GP scheme in the recurrence and metastasis of NPC status of first-line chemotherapy was confirmed in a randomized clinical trial III period, and GP solutions with the PF group of PFS difference were statistically significant (7.0 *vs.* 5.6 months, $p<0.0001$)[19]. Zheng et al[20] analyzed 604 cases of two-dimensional radiotherapy or IMRT on locally advanced nasopharyngeal carcinoma patients, and found that although increased induction chemotherapy did not achieve a survival benefit, the GP program of induction chemotherapy was an independent prognostic factor the OS (p = 0.038), and the absence of distant metastasis has a tendency to improve survival (p = 0.109). This suggested that the GP scheme as induction chemotherapy in the treatment of patients with locally advanced nasopharyngeal carcinoma may be superior to the TP or PF schemes. Similar results were also reported by Zhao et al[21], suggesting that in the subgroup analysis of nasopharyngeal carcinoma patients in non-endemic areas, there was a statistically significant difference in OS between male patients or patients with bilateral cervical lymph node metastasis after chemotherapy induced by the GP regimen and the TP regimen or the PF regimen. Wu et al[22] published a GP plan joint IMRT treatment of locally advanced NPC II phase of clinical trial results which reported that five years local control, regional control, OS, and no distant metastasis survival rate were 93.2%, 92.3%, 89.0% and 82.1% respectively, suggesting that the GP scheme combined with IMRT is a safe and effective treatment strategy.

The toxic side effects of treatment may limit its efficacy in patients with locally advanced NPC. In this study, both treatment regimens were well tolerated. Specific adverse events were associated with both treatment regiments. Neutropenia, leukopenia, anemia, and other common acute adverse reactions of chemotherapy were mainly observed, while thrombocytopenia was more common in the GP group (15.1%) than in the TPF group (7.8%). The additional of gemcitabine may be the cause of the higher thrombocytopenia rates, as it causes bone marrow suppression[23].

Conclusions

In our study, PSM was used to balance the variables that may influence the outcomes between the groups to obtain more credible research results. Using GP as the IC treatment regimen improved patients' OS and DFS for 5 years, and no serious adverse events occurred. GP can be used as an option to treat locally advanced NPC.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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