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ORIGINAL ARTICLE

# Gemcitabine plus cisplatin versus fluorouracil plus cisplatin as a first-line concurrent chemotherapy regimen in nasopharyngeal carcinoma: a prospective, multi-institution, randomized controlled phase II study

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## Abstract

**Background** The objective of this study was to evaluate the efficacy and safety of gemcitabine plus cisplatin concurrent chemoradiotherapy (CCRT) in patients with nasopharyngeal carcinoma.

**Method** Patients with NPC were randomly assigned to the gemcitabine plus cisplatin (GP) group or fluorouracil plus cisplatin (PF) group. Primary end-point was disease-free survival (DFS); secondary endpoints: overall survival, distant metastasis-free survival (DMFS), locoregional relapse-free survival, and treatment-related adverse events.

**Results** Seventy-six patients were prospectively enrolled and the median follow-up time was 41 months (9–61 months). Three-year DFS were similar between the GP and PF groups (73.7% vs. 60.5%, HR 0.66, 95% CI 0.30–1.44; $P=0.30$). Distant metastasis was the most common failure form in PF compared with GP ($P=0.034$). Three-year DMFS was significantly better in the GP group than PF group (89.5% vs. 71.1%, $P=0.045$). Grade 3–4 gastrointestinal toxicities (vomiting and diarrhea) were significantly more common in the PF group; grade 3–4 neutropenia and thrombocytopenia were more common in the GP group.

**Conclusion** Gemcitabine plus cisplatin could be used as an alternative regimen in CCRT for nasopharyngeal carcinoma.

**Keywords** Nasopharyngeal carcinoma · Concurrent chemoradiotherapy · Gemcitabine · Cisplatin · Chemotherapy regimen

## Introduction

Nasopharyngeal carcinoma (NPC) has an extremely high incidence in Southeast Asia, particularly Southern China [1, 2]. Concurrent chemoradiotherapy with single cisplatin is the standard of treatment for patients with NPC [3]. Interestingly, with the appearance of new chemotherapy drugs [4], these were proved effective of platinum-based doublet chemotherapy in combination with radiotherapy in head-and-neck cancer including NPC [5, 6]. However, severe toxicities, such as gastrointestinal toxicities, hematologic toxicities and oral mucositis, limited the use of concurrent doublet chemoradiotherapy [7]. Therefore, optimizing the drug combinations and schedules has become the focus of research to reduce toxicities during CCRT.

Gemcitabine, an analog of deoxycytidine that inhibits DNA synthesis, has a high treatment efficacy in several tumor types, including lung cancer [8] and head-and-neck

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cancers [9], and is also reported to provide relatively high response rates in NPC [10]. In a Phase I study, Gustavo et al. [9]. found that gemcitabine provided a potent radiosensitizing effect in locally advanced head-and-neck cancer. Moreover, gemcitabine plus cisplatin (GP) is widely used in metastatic NPC due to its efficacy and safety [11, 12]. In vitro evidence suggests that gemcitabine and cisplatin act synergistically and have non-overlapping toxicity profiles [10]. However, it is not clear whether GP-based first-line CCRT provides a therapeutic benefit or reduces toxicities in NPC.

Therefore, we designed an open-label, multicenter, phase II, randomized controlled trial to compare the efficacy and safety of first-line CCRT based on GP with first-line CCRT based on 5-fluorouracil (5-FU) and cisplatin in locoregionally advanced NPC..

## Patients and methods

### Patients

Eligible patients had histologically proven non-keratinizing or undifferentiated (WHO classification) stage II–IVB NPC (the AJCC staging system, 7th edition, 2010), a Karnofsky performance status (KPS) score of at least 80 and good general condition, adequate bone marrow reserve (including white cell count $\geq 4.0\times10^9$/L, platelet count $\geq 100\times10^9$/L, hemoglobin $\geq 100$ g/L), adequate liver and renal function (including creatinine clearance rate $\geq 60$ ml/min), and no obvious electrocardiogram abnormalities. Exclusion criteria included age > 60 years(more than 60 years old as elderly NPC [13]) or < 18 years; KPS score < 80; abnormal liver or renal function; heart disease or dysfunction; previous chemotherapy, radiotherapy or surgery to the primary tumor; metastatic lesions and other malignancies.

All participants provided written informed consent before random assignment. The protocol was approved by the institutional review board of Guilin Medical University. This study was registered in the Chinese Clinical Trial Registry (registration number: ChiCTR- TRC-12002421).

### Study design

This is a prospective, multi-institution, randomized controlled phase II study. Recruitment and inclusion of patients are shown in Fig. 1. The 76 patients were assigned 1:1 using the random assignment approach (computer-generated random number codes) to receive CCRT based on either GP (38 patients) or PF (38 patients). The two treatment groups were well balanced in terms of baseline clinical features and tumor characteristics, such as age, sex and clinical stage (Table 1).

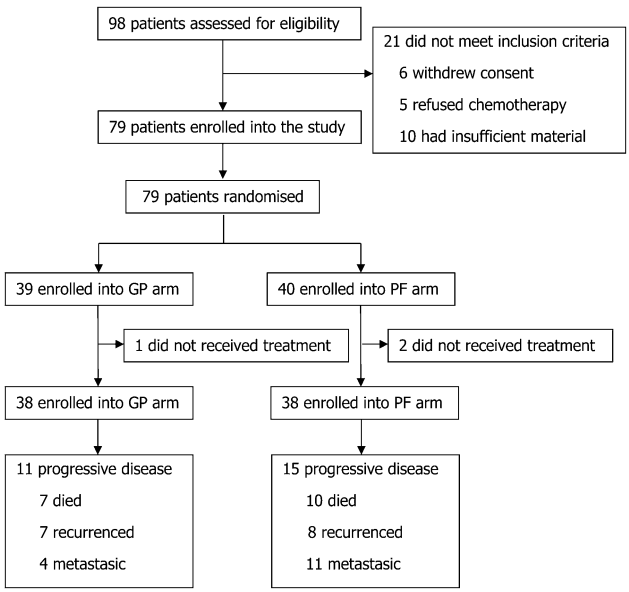


**Fig. 1** Recruitment and inclusion of patients with locoregionally advanced nasopharyngeal carcinoma to the study

**Table 1** Clinicopathological features of the patients

| Feature | GP group ($n=38$) | PF group ($n=38$) | *P* |
|---|---|---|---|
| Sex | | | |
| Male | 26 (68.4%) | 29 (76.3%) | 0.815 |
| Female | 12 (31.6%) | 9 (23.7%) | |
| Age (years) | | | |
| < 45 | 15 (39.5%) | 16 (42.1%) | 0.442 |
| > 45 | 23 (60.5%) | 22 (57.9%) | |
| *T* classification | | | |
| *T*1 | 3 (7.9%) | 4 (10.5%) | 0.824 |
| *T*2 | 6 (15.8%) | 8 (21.1%) | |
| *T*3 | 18 (47.4%) | 18 (47.4%) | |
| *T*4 | 11 (28.9%) | 8 (21.1%) | |
| *N* classification | | | |
| *N*0 | 2 (5.3%) | 3 (7.9%) | 0.923 |
| *N*1 | 8 (21.1%) | 8 (21.1%) | |
| *N*2 | 26 (68.4%) | 24 (63.2%) | |
| *N*3 | 2 (5.3%) | 3 (7.9%) | |
| Stage | | | |
| II | 3 (7.9%) | 4 (10.5%) | 0.904 |
| III | 23(60.5%) | 23 (60.5%) | |
| IVA | 10(26.3%) | 8 (21.1%) | |
| IVB | 2 (5.3%) | 3 (7.9%) | |
| Radiotherapy technique | | | |
| 2DRT | 16 (42.1%) | 16 (42.1%) | 0.580 |
| 3DCRT | 4 (10.5%) | 7 (18.4%) | |
| IMRT | 18 (47.4%) | 15 (39.5%) | |

*GP* Gemcitabine plus cisplatin, *PF* fluorouracil plus cisplatin, *2DRT* two-dimensional radiotherapy, *3DCRT* three-dimensional conformal radiotherapy, *IMRT* intensity-modulated radiation therapy

### Pretreatment evaluation

Before treatment, all patients underwent a complete physical examination, medical history and blood tests. The physical examination included chest computed tomography (CT), abdominal ultrasonography, bone radionuclide scan and magnetic resonance imaging (MRI) of the nasopharynx and neck. Before radiation therapy, if deemed necessary all patients attended a dentist.

### Radiotherapy

Radiotherapy was administered via define (2DRT), define (3DCRT) or intensity-modulated radiotherapy (IMRT) using 6-MV linear accelerators. All radiotherapy plans were formulated by an experienced expert team. CT/MRI scans were used to define target volumes.

For 2DRT or 3DCRT, 66–70 Gy was delivered to the primary tumor and metastatic cervical lymph nodes. Conventional fractionated radiotherapy was delivered in 2 Gy fractions, once daily, five times per week over 7 weeks.

For IMRT, the primary tumor and metastatic cervical lymph nodes were defined as the gross tumor volume (GTV) and received a total of 66–70 Gy. The clinical target volume (CTV) was divided into the high-risk area (CTV1) and low-risk area (CTV2), which received at least 60–66 Gy and 50–54 Gy, respectively, and included the entire nasopharyngeal cavity, clivus, parapharyngeal space, retropharyngeal nodal regions, skull base, sphenoid sinus, pterygoid fossae and posterior one-third of the nasal cavity and nodal levels I–V. IMRT was delivered as one fraction daily, 5 days per week.

### Chemotherapy

Chemotherapy started on day one of radiotherapy. Two cycles of chemotherapy were planned. The clinical toxicities were assessed for every week such as physical examination or laboratory tests. The GP group received 1000 mg/m$^2$ gemcitabine intravenously on days 1 and 8 and a total dose of 75 mg/m$^2$ cisplatin over 1-h infusions on days 1–3, every 3 weeks. The PF group received a continuous infusion (120 h infusion) of 750 mg/m$^2$ fluorouracil per day on days 1–5 and 75 mg/m$^2$ cisplatin for 3 days, every 3 weeks. The RT dose was 66–70 Gy. Antiemetic drugs such as 5-HT$_3$-receptor antagonist, metoclopramide, and dexamethasone were used to prevent chemotherapy-induced nausea and vomiting during CCRT.

### Response and toxicity evaluation

All patients underwent regular physical examinations and were contacted by phone to assess toxicities. All participants ($n = 76$) were assessed 3 months after radiotherapy via a physical examination and the imaging at follow-up. The imaging of follow-up included chest computed tomography (CT), abdominal ultrasonography, bone radionuclide scan and magnetic resonance imaging (MRI) of the nasopharynx and neck. The bone radionuclide scan should be made if bone metastases were suspected; and the MRI or CT should be made if distant metastases were suspected. If necessary, the puncture biopsy under CT guidance could be made. Tumor response was classified using the Response Evaluation Criteria in Solid Tumors (version 1.0); treatment toxicities were graded in accordance with the Common Terminology Criteria for Adverse Events (version 3.0). All participants were followed up until death or for at least 3 years.

### Statistical analysis and follow-up

After treatment, follow-up was performed every 3 months in the first and second years and every 6 months thereafter; recurrence, progression, metastasis or death was recorded. To determine the appropriate study sample size, as we hypothesized, we expected that the three-year DFS was 61% in PF group [14] and a 10% increase in the DFS in GP group. To detect this difference (with one-sided alpha 15%, power 80%), randomization of a total of 66 patients (33 per group) was required. To allow for a 10% rate of patients lost to follow-up, at least 73 patients should have been enrolled. Time of follow-up duration was measured from randomization to day of last examination or death for overall survival (OS); to first distant metastasis for distant metastasis-free survival (DMFS); to treatment failure or death from any case for disease-free survival (DFS); and locoregional progression for locoregional relapse-free survival (LRRFS).

The *t* test or Chi-square test was used to compare clinical characteristics; Chi-square test or Fisher's exact test, to compare responses and toxicities. OS, DFS, LRRFS and DMFS were calculated using the Kaplan–Meier method and compared using the log-rank test. Response rates and acute/subacute toxicities were analyzed on an intention-to-treat basis. Statistical analyses were conducted using SPSS (version 13.0). Two-sided $P$ values $< 0.05$ were considered significant.

## Results

### Patient characterization and follow-up

Between October 1, 2010 and October 1, 2014, 98 patients were screened for enrolment at the Affiliated Hospital of Guilin Medical University, the Affiliated Hospital of Youjiang Medical University for Nationalities and the Second People's Hospital of Yulin and the People's Hospital of

Laibin. 76 (78%) of these patients (55 males, 21 female) with an average age of 46 years (range 24–60 years) met all eligibility criteria and were randomly assigned to this study. The two treatment groups were well balanced in terms of baseline clinical features and tumor characteristics, such as age, sex and clinical stage (Table 1). Median follow-up time was 41 months (9–61 months); all patients ($n=76$) had complete follow-up data.

## Treatment compliance

All 76 patients received concurrent radiotherapy and chemotherapy. Patients received two cycles of chemotherapy during radiotherapy. In the GP group, all patients finished their scheduled treatment; 4/38 (10.5%) patients had delayed concurrent chemotherapy because of grade 3–4 leukopenia/neutropenia. In the PF group, all patients finished their scheduled treatment; 2/38 (5.26%) had delayed concurrent chemotherapy because of intolerable gastrointestinal and mucositis toxicities, and resumed treatment when their toxicities were in remission.

## Response, survival and failure

Treatment response was assessed at 3 months after the end of RT for all patients. The complete response (CR) rate was 100% for both treatment groups. The GP group achieved significantly better DMFS than the PF group (89.5% vs. 71.1%; HR 0.33, 95% CI 0.11–1.03; $P=0.045$). Three-year overall survival (OS), disease-free survival (DFS), and locoregional relapse-free survival (LRRFS) were similar between the GP and PF groups (81.6% vs. 74%, HR 0.69, 95% CI 0.26–1.82; $P=0.45$; 73.7% vs. 60.5%, HR 0.66, 95% CI 0.30–1.44; $P=0.30$; 81.6% vs. 78.9%, HR 0.84, 95% CI 0.30–2.32; $P=0.74$, respectively; Fig. 2). Four (4/38; 10.53%) patients in the GP group developed metastatic disease after curative radiotherapy (one to bone, one to lung and two to liver, including one multiple organ metastasis) compared to eleven patients (11/38; 28.95%) in the PF group (four to bone, five to lung and three to liver, including three with multiple organ metastasis). Seven patients (7/38; 18.42%) in the GP group developed local recurrence after curative radiotherapy (six in nasopharynx, one in neck) compared to eight patients (8/38; 21.05%) in the PF group (seven in nasopharynx, three in neck, including two combined nasopharynx/neck). No patients in the GP group and four patients (4/38; 10.53%)

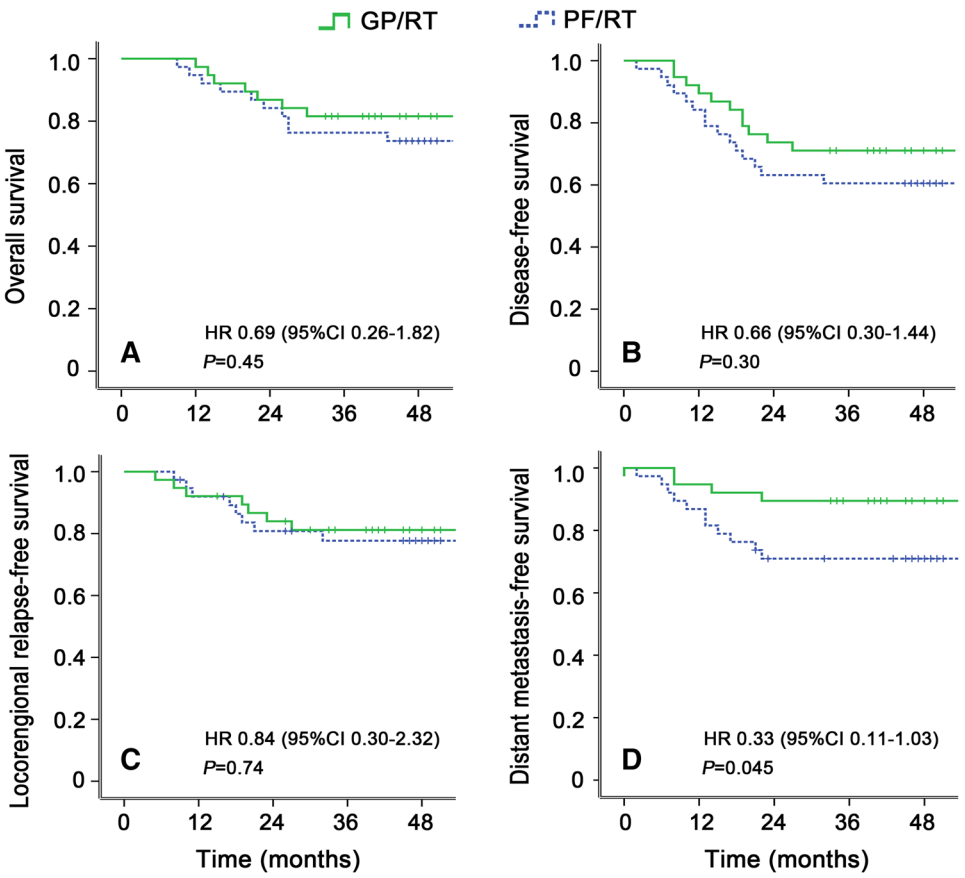


**Fig. 2** Kaplan–Meier survival curves for patients with locoregionally advanced nasopharyngeal carcinoma in the GP group and PF group. **a** Overall survival; **b** disease-free survival; **c** locoregional relapse-free survival; and **d** distant metastasis-free survival

in the PF group developed both distant metastasis and recurrence (Table 2).

## Toxicities

No deaths occurred during treatment in either group. Routine blood tests were conducted every week, and liver and kidney function was examined every 2 weeks during treatment. As anticipated, the incidences of grade III–IV neutropenia and thrombocytopenia were higher in the GP group than the PF group (50% vs. 26.3%, $P=0.024$, and 0.053% vs. 0, $P=0.000$, respectively). With respect to non-hematologic adverse events, grade III gastrointestinal toxicities such as vomiting were less frequent in the GP group than the PF group (13% vs. 29%, $P=0.042$), and diarrhea was more frequent in the PF group (7.9% vs. 28.9%, $P=0.000$). Grade III mucositis was less frequent in the GP group than the PF group (34% vs. 61%, $P=0.046$). The toxicities are listed in Table 3.

**Table 2** Patterns of failure

| Failure site(s) | GP group ($n=38$) | PF group ($n=38$) | *P* |
|---|---|---|---|
| Total failure in metastasis | 4 | 11 | 0.034 |
| Bone metastasis | 1 | 4 | |
| Lung metastasis | 1 | 5 | |
| Liver metastasis | 2 | 3 | |
| Multiple organs | 1 | 3 | |
| Total failure in recurrence | 7 | 8 | 0.773 |
| Nasopharynx | 6 | 7 | |
| Neck | 1 | 3 | |
| Metastasis + recurrence | 0 | 4 | 0.115 |

*GP group* Gemcitabine plus cisplatin, *PF group* fluorouracil plus cisplatin

## Discussion

The platinum-based doublet chemotherapy is commonly administered during CCRT for NPC. Huang et al. [17] have demonstrated that concurrent multiagent chemotherapy (taxanes plus platinum) and radiation were feasible and could be delivered to patients with high compliance rates for patients of the NPC. Another trial had demonstrated that the addition of doublet chemotherapy [platinum and 5-fluorouracil (5-FU)] to radiotherapy could significantly improve survival in NPC patients [6, 7]. However, data comparisons of platinum-based doublets chemotherapy regimens, with regard to clinical toxicity and survival, were not clear. In this multicenter, randomized phase II study, a number of treatment outcomes were better in the GP group than the PF group; in particular, DMFS was significantly prolonged. Thus, GP may represent a superior combination for NPC as it was well tolerated with manageable toxicities.

In our study, three-year overall survival were similar between the GP and PF groups (81.6% vs 74%). Compared with single-agent cisplatin of study of Edwin P. Hui [15], patients received concurrent cisplatin chemotherapy (40 mg/$m^2$/w) combined with radiation. The three-year overall survival was 67.70%. Another study of single agent cisplatin reported that the three-year OS and DFS were 80% and 72%, respectively [16]. The 2-year cumulative incidence (including of recurrent and metastatic) of relapse was 13%. Our results were superior to most studies.

To date, gemcitabine-based regimens have been pivotal in the treatment of NPC. Gemcitabine-based chemotherapy in metastatic nasopharyngeal carcinoma and

**Table 3** Treatment-related toxicities

| Toxicity | GP group ($n=38$) | | | | PF group ($n=38$) | | | | *P* |
|---|---|---|---|---|---|---|---|---|---|
| | Grade 1 | Grade 2 | Grade 3 | Grade 4 | Grade 1 | Grade 2 | Grade 3 | Grade 4 | |
| Mucositis (radiation related) | 5 | 20 | 13 | 0 | 2 | 13 | 23 | 0 | **0.046** |
| Skin reaction (radiation related) | 8 | 28 | 2 | 0 | 5 | 30 | 3 | 0 | 0.618 |
| Vomiting | 15 | 18 | 5 | 0 | 6 | 21 | 11 | 0 | **0.042** |
| Nausea | 5 | 20 | 13 | 0 | 2 | 18 | 18 | 0 | 0.333 |
| Leukopenia/neutropenia | 5 | 10 | 11 | 6 | 5 | 18 | 9 | 1 | **0.024** |
| Thrombocytopenia | 9 | 4 | 2 | 0 | 3 | 0 | 0 | 0 | **0.000** |
| Anemia | 8 | 6 | 13 | 0 | 13 | 7 | 0 | 0 | **0.001** |
| Diarrhea | 3 | 0 | 0 | 0 | 8 | 3 | 0 | 0 | **0.000** |
| Dry mouth | 7 | 31 | 0 | 0 | 6 | 32 | 0 | 0 | 1.000 |
| Hepatotoxicity | 1 | 0 | 0 | 0 | 3 | 0 | 0 | 0 | – |
| Nephrotoxicity | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | – |

$P<0.05$ indicates a statistically significant difference between the PF regimen and GP regimen, Chi-square test or Fisher's exact test

gemcitabine-based induction chemotherapy, adjuvant chemotherapy and immunotherapy in advanced NPC have reasonable efficacy and significantly improve quality of life. Zhang et al. [11]. compared gemcitabine and fluorouracil regimens in 362 patients with recurrent or metastatic NPC in a phase III trial, and reported that gemcitabine plus cisplatin regimen significantly improved OS and PFS. Similarly, six studies [18–23] in metastatic or recurrent NPC showed that gemcitabine improved efficacy and reduced toxicities, indicating that gemcitabine reduces the risk of distant metastases and improves survival. And Zhao et al. [24] and Lim et al. [25] reported that gemcitabine-based induction chemotherapy improved DFS and OS in patients with advanced local nasopharyngeal carcinoma. Moreover, Yin Li et al. [23] reported gemcitabine combination immunotherapy and Cong Xue et al. [26] reported gemcitabine combination targeted agent, confirming the potential therapeutic efficacy of gemcitabine chemotherapy. Similar to these studies, we also observed that gemcitabine-based CCRT provided a survival benefit in this multicenter, randomized phase II study. DMFS was significantly better in the GP group, with 18.4% lower risk of distant metastasis than the PF group. These results are encouraging, as distant metastasis is currently the main cause of treatment failure in NPC.

There are a number of reasons why gemcitabine could reduce the risk of distant metastasis and improve survival. Firstly, gemcitabine plus cisplatin exerts synergistic cytotoxic effects with non-overlapping toxicities in vitro [9, 10, 19]. Secondly, gemcitabine leads to termination of elongation/repair of DNA polymerase chains, and has a broad spectrum of activity in various solid tumors [9]. Thirdly, gemcitabine may also affect Epstein–Barr virus (EBV), a major prognostic factor in NPC, by suppressing the immunosuppressive microenvironment to enhance the anti-tumor immune response [27]. Therefore, gemcitabine combined with cisplatin could represent a better first-line CCRT regimen than cisplatin and fluorouracil in NPC, and this regimen deserves to be investigated further in clinical trials.

Considering the toxicities of the doublet chemotherapy in CCRT, our exclusion criteria have selected 60 years of age as the cutoff point in our study, because the patients aged > 60 years may have received fewer number cycles or lower doses of chemotherapy owing to poor tolerance, complication, decline in organ function [13]. In terms of tolerability, the requirement for deep-vein catheterization and continuous venous infusion limits the fluorouracil regimen, while GP has a shorter administration time, making patients more willing to cooperate with treatment. Moreover, as expected, GP led to higher frequencies of neutropenia and thrombocytopenia than PF ($P = 0.024$). However, GP did not lead to more serious infectious complications if the patients received prophylactic antibiotics. In this trial, gastrointestinal toxicities (vomiting and diarrhea) during CCRT were a key risk factor for treatment delays. The incidence of diarrhea for PF was high (28.9%), even though antiemetics were routinely prescribed. However, gastrointestinal adverse events can cause major distress and were more frequent in the PF group. The incidence of serious vomiting was 13% for GP and 29% for PF. Due to its lower rate of gastrointestinal toxicities, GP may be more suitable and preferable as a first-line treatment. Additionally, the incidence of oral mucositis was lower for GP than PF (34% vs. 61%), meaning that GP had excellent treatment compliance. Patients can eat better and are more willing to cooperate with treatment, if the oral mucosa is less affected. Accordingly, patients can maintain a good body weight during treatment, which is important as weight loss during therapy is a negative prognostic factor in malignant disease [28]. Compared to other studies, our study showed that this side effect is tolerable because we decreased cumulative dose cisplatin to reduce the potentially additive side effects of CCRT and the patients we enrolled were relatively young(age < 60 years), with a high KPS score and good support care. Accordingly, GP regimens are a feasible and effective choice for patients with NPC.

Despite our best efforts, the inherent limitations of this study need to be acknowledged. The main limitation is the relatively small sample size, which means we cannot exclude the possibility of unpredictable factors. Second, nearly half of patients received two-dimensional radiotherapy. Therefore, the efficacy of the GP regimen should be investigated in a phase III randomized trial of patients undergoing IMRT.

## Conclusion

Gemcitabine plus cisplatin could be used as an alternative two drugs regimen in CCRT for nasopharyngeal carcinoma. Our findings support further evaluation of the GP regimen in phase III trials.

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### Compliance with ethical standards

**Conflict of interest** The authors have no conflict of interest for this manuscript.

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