Gemcitabine plus cisplatin versus fluorouracil plus cisplatin in recurrent or metastatic nasopharyngeal carcinoma: a multicentre, randomised, open-label, phase 3 trial

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Summary

Background **Outcomes are poor for patients with recurrent or metastatic nasopharyngeal carcinoma and no well established first-line chemotherapy is available for the disease. We compared the efficacy and safety of gemcitabine plus cisplatin versus fluorouracil plus cisplatin in patients with recurrent or metastatic nasopharyngeal carcinoma.**

Methods **In this multicentre, randomised, open-label, phase 3 trial, patients with recurrent or metastatic nasopharyngeal carcinoma were recruited from 22 hospitals in China. Key inclusion criteria were Eastern Cooperative Oncology Group performance status of 0 or 1, adequate organ function, and measurable lesions according to Response Evaluation Criteria in Solid Tumors version 1.1. Patients were randomly assigned in a 1:1 ratio to receive either gemcitabine (1 g/m² intravenously on days 1 and 8) and cisplatin (80 mg/m² intravenously on day 1), or fluorouracil (4 g/m² in continuous intravenous infusion over 96 h) and cisplatin (80 mg/m² on day 1 given intravenously) once every 3 weeks for a maximum of six cycles. The randomisation was done centrally via an interactive phone response system using block randomisation with a size of six. The primary endpoint was progression-free survival assessed by the independent image committee in the intention-to-treat population. Safety analyses were done in patients who received at least one cycle of study drug. This study is ongoing and is registered with ClinicalTrials.gov, number NCT01528618.**

Findings **Between Feb 20, 2012, and Oct 30, 2015, 362 patients were randomly assigned to a group (181 to the gemcitabine [plus cisplatin] group and 181 to the fluorouracil [plus cisplatin] group). Median follow-up time for progression-free survival was 19·4 months (IQR 12·1–35·6). The median progression-free survival was 7·0 months (4·4–10·9) in the gemcitabine group and 5·6 months (3·0–7·0) in the fluorouracil group (hazard ratio [HR] 0·55 [95% CI 0·44–0·68]; p<0·0001). A total of 180 patients in the gemcitabine group and 173 patients in the fluorouracil group were included in the safety analysis. Significantly different treatment-related grade 3 or 4 adverse events between the gemcitabine and fluorouracil groups were leucopenia (52 [29%] *vs* 15 [9%]; <0·0001), neutropenia (41 [23%] *vs* 23 [13%]; p=0·0251), thrombocytopenia (24 [13%] *vs* three [2%]; p=0·0007), and mucosal inflammation (0 *vs* 25 [14%]; <0·0001). Serious treatment-related adverse events occurred in seven (4%) patients in the gemcitabine group and ten (6%) in the fluorouracil group. Six (3%) patients in the gemcitabine group and 14 (8%) patients in the fluorouracil group discontinued treatment because of drug-related adverse events. No treatment-related deaths occurred in either group.**

Interpretation **Gemcitabine plus cisplatin prolongs progression-free survival in patients with recurrent or metastatic nasopharyngeal carcinoma. The results establish gemcitabine plus cisplatin as the standard first-line treatment option for this population.**

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Introduction

Nasopharyngeal carcinoma is a common type of malignancy in south China and southeastern Asia.[1,2] About 86 000 incidence cases and 50 000 deaths attributable to the disease occur annually worldwide,[1] the racial and geographic distributions of which are greatly heterogeneous.[3] On the basis of high-level evidence, radiotherapy or chemoradiotherapy has become the primary treatment for early or locoregionally advanced nasopharyngeal carcinoma,[4] producing a 5 year survival rate of about 85%.[5] However, the great potentiality of systemic dissemination remains the major reason of treatment failure for these patients.[6,7] Additionally, about 15% of patients with nasopharyngeal carcinoma present with distant metastases at primary diagnosis.[8] The outcome for patients with recurrent or primary metastatic nasopharyngeal carcinoma is very poor, with a median overall survival of about 20 months.[9]

Nasopharyngeal carcinoma is a highly chemosensitive cancer. Platinum-containing doublet chemotherapy is generally regarded as the standard treatment for patients with recurrent or metastatic nasopharyngeal

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Research in context

Evidence before this study

Nasopharyngeal carcinoma is a highly chemosensitive tumour, with response rates as high as 80%. Platinum-containing doublet chemotherapy regimens are generally regarded as the standard first-line therapy in recurrent or metastatic disease. We searched PubMed for clinical trials published in any language between Jan 1, 1980, and July 1, 2016, using the search terms "nasopharyngeal carcinoma", "metastatic or recurrent", and "chemotherapy". We also searched the reference lists of retrieved articles. A wide range of chemotherapy drugs have shown antitumour activity in patients with recurrent or metastatic nasopharyngeal carcinomas; these include the platinum compounds (cisplatin, carboplatin, oxaliplatin), fluorouracil (including capecitabine), methotrexate, taxanes (paclitaxel, docetaxel), gemcitabine, bleomycin, ifosfamide, anthracyclines, irinotecan, and vinorelbine. Our scientific literature review found no other head-to-head trials in patients with recurrent or metastatic nasopharyngeal carcinoma. The available evidence was based on many phase 2 trials, with the sample size ranging from 14 to 75 and including patients with various treatment backgrounds.

Added value of this study

To the best of our knowledge, this study is the first randomised, multicentre trial comparing two chemotherapy regimens in recurrent or metastatic nasopharyngeal carcinoma that provides evidence of efficacy and safety in a head-to-head comparison. The results of the study show that gemcitabine plus cisplatin outperforms fluorouracil plus cisplatin over a range of clinical endpoints, including the primary endpoint progression-free survival, and the proportion of patients achieving an objective response. A preliminary analysis of overall survival suggested that there was also a significant improvement with the gemcitabine-based combination. Gemcitabine plus cisplatin was associated with increased risk of haematological adverse events whereas fluorouracil plus cisplatin led to more mucositis. Both regimens have predictable and manageable adverse event profiles.

Implications of all the available evidence

The study suggests that gemcitabine plus cisplatin is more effective than fluorouracil plus cisplatin in the treatment of recurrent or metastatic nasopharyngeal carcinoma. The results could establish gemcitabine plus cisplatin as the current standard first-line treatment option for this population.

carcinoma, even though it has never been directly compared with supportive care.[10,11] Until now, no randomised trials have defined the optimum regimens. Whether a survival difference exists among patients receiving different protocols remains unknown. At present, cisplatin plus continuous intravenous infusion of fluorouracil is widely used in patients with recurrent or metastatic nasopharyngeal carcinoma, with a response rate of 40–65%.[12–14] However, the short duration of response, common mucosal complications, and the requirement of deep vein catheterisation remain the major limitations of the fluorouracil plus cisplatin regimen. Therefore, finding new combination chemotherapies to prolong survival of patients with recurrent or metastatic nasopharyngeal carcinoma with acceptable toxicity is of importance.

Gemcitabine is a pyrimidine analogue and a ribonucleotide reductase inhibitor that has a broad spectrum of antitumour activity. The synergistic cytotoxic effects between gemcitabine and cisplatin seen in vitro have made it a promising combination regimen in oncological practice.[15] Several phase 2 trials[16–18] suggested that gemcitabine has satisfactory efficacy and tolerable toxicities in patients with nasopharyngeal carcinoma. However, the numbers of patients enrolled in these studies were too small to draw solid conclusions. We therefore did this head-to-head, randomised, phase 3 trial to compare the efficacy and safety of gemcitabine plus cisplatin versus fluorouracil plus cisplatin in patients with recurrent or metastatic nasopharyngeal carcinoma in the first-line setting.

Methods

Study design and participants

This is a multicentre, randomised, open-label, phase 3 trial, done in 22 hospitals in China (appendix pp 4, 5). Investigators at participating centres enrolled patients with histologically or cytologically confirmed nasopharyngeal carcinoma. The histological subtype of nasopharyngeal carcinoma was categorised according to the WHO classification of tumours. Type I is keratinising squamous-cell carcinoma. Type II is differentiated non-keratinising carcinoma. Type III is undifferentiated non-keratinising carcinoma.

Other eligibility criteria were that the patient has metastatic disease after curative radiotherapy, or local recurrence after curative radiotherapy, which is unsuitable for local treatment or is primarily metastatic (stage IVC as defined by the International Union Against Cancer and American Joint Committee on Cancer staging system for nasopharyngeal carcinoma, seventh edition); has not received any previous systemic chemotherapy for recurrent or metastatic disease; has an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1; is aged 18 years or older; has adequate organ function (white blood cell count of $4{\cdot}0\times10^9$ per L or more; absolute neutrophil of $2{\cdot}0\times10^9$ per L or more; haemoglobin concentrations of at least 90 g/L; platelet cell count of 100×10^9 per L or more; aspartate transaminase and alanine transaminase of less than 2·5 times the upper limit of the normal value; and creatinine clearance rate of more than 60 mL/min); has at least one measurable lesion

according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1; lesions located in a previously irradiated area were deemed unmeasurable); has an estimated life expectancy of 12 weeks or more; has provided written informed consent; and is amenable for regular follow-up.

Patients met exclusion criteria (appendix pp 1–3) if they were suitable for local treatment (except for palliative, limited-field radiation to non-target metastatic lesions); had previously received induction, adjuvant, or concurrent chemotherapy, chemoradiotherapy, or radiotherapy (however, were permitted if at least 6 months had elapsed between last treatment and study enrolment); had a serious infection (grade 2 or higher according to the National Cancer Institute Common Toxicity Criteria for Adverse Events [NCI-CTCAE], version 3.0); had CNS metastases; had a life-threatening medical disorder; had bone-only metastasis; were pregnant or breastfeeding; had pre-existing peripheral neuropathy (grade 2 or higher according to NCI-CTCAE 3.0); had other invasive malignant diseases within the past 5 years, except excised basal-cell skin carcinoma, cervical carcinoma in situ, superficial bladder tumours (Ta, Tis, and T1), or other cancers curatively treated more than 3 years before study entry; or had serious comorbidities.

The study protocol was approved by the ethics committee of Sun Yat-sen University Cancer Center and each participating institution. The study was done in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines as defined by the International Conference on Harmonization. All patients provided written informed consent.

Randomisation and masking

We randomly assigned eligible patients (1:1) to receive either gemcitabine plus cisplatin (gemcitabine group) or fluorouracil plus cisplatin (fluorouracil group). Randomisation was done centrally by the contract research organisation (H&J, Beijing, China) with a block size of six via an interactive phone response system, with no stratification factors. Investigators assessed the eligibility of a patient. When the inclusion criteria were met, the patient's information would be sent to an outside contract research organisation (H&J, Beijing, China). The study coordinator sent the allocated treatment back to the investigators by telephone. Masking was not done in this trial. Patients, investigators, other treating oncologists, and staff at participating centres were aware of the treatment allocation. However, the central imaging group and statisticians were blinded.

Procedures

Patients assigned to the gemcitabine group received intravenous gemcitabine at 1 g/m² over 30 min on days 1 and 8, and cisplatin at 80 mg/m² for 4 h on day 1. Patients assigned to the fluorouracil regimens received fluorouracil at 4 g/m² via continuous intravenous infusion over 96 h and cisplatin at 80 mg/m² for 4 h on day 1 intravenously. Patients in both groups received allocated treatment once every 3 weeks for a maximum of six cycles, or until disease progression, death, occurrence of intolerable toxicities, or at patients' request to stop. Use of any other anticancer drugs was not allowed before protocol-defined disease progression.

See Online for appendix

To prevent the nephrotoxic effect of cisplatin, we applied 3 day hydration during the administration of cisplatin (on days 0–2) and used diuretics (mannitol and furosemide) on the day of cisplatin administration. We used antiemetic drugs such as 5-HT_3-receptor antagonist, metoclopramide, and dexamethasone to prevent chemotherapy-induced nausea and vomiting. Prophylactic granulocyte-colony stimulating factors were not allowed.

We applied the following recommendations for dose reductions: in patients who had grade 3 or 4 haematological, grade 3 or 4 non-haematological, or other protocol-specified toxic effects, gemcitabine, fluorouracil, and cisplatin treatments were interrupted. If the toxic effects resolved to a grade lower than 2, the dose of gemcitabine or fluorouracil was restarted at 80% of the dose at the last appearance of the toxic effects. For patients with neutropenia, day 8 gemcitabine could be given at a reduced dose or postponed for up to 5 days to allow recovery, otherwise it was discontinued. Only two dose reductions were allowed for gemcitabine or fluorouracil in both groups. For cisplatin, dose modification was based on the prechemotherapy creatinine clearance rate (CCR) in every cycle, calculated with Cockcroft formulation. If CCR was higher than or equal to 60 mL/min, cisplatin was given at full dose. If CCR was between 41 mL/min and 59 mL/min, an equal dose to the CCR value (mg/m²) was applied. If CCR was less than 41 mL/min, cisplatin was stopped in the current cycle and the dose of cisplatin was evaluated in the next cycle.

We removed patients from the study if they had progressive disease, developed protocol-specified unacceptable side-effects, initiated another antitumour treatment, withdrew consent, or if their assigned treatment was delayed for more than 2 weeks. Treatment was permanently discontinued if more than two dose modifications were needed.

Before enrolment, each patient provided a detailed medical history and underwent physical examinations, along with complete blood cell count, biochemical laboratory test, nasopharyngeal and neck MRI, chest and upper abdomen CT scan, and bone scintigraphy or ^{18}F-fluorodeoxyglucose PET scan. Epstein-Barr virus (EBV) titres were optional, depending on the laboratory availability of the participating centres. Patients received a routine blood test and biochemical laboratory test at least every 2 weeks during study treatment.

Tumour response was assessed by imaging according to RECIST version 1.1 by the independent image committee every two cycles until disease progression.

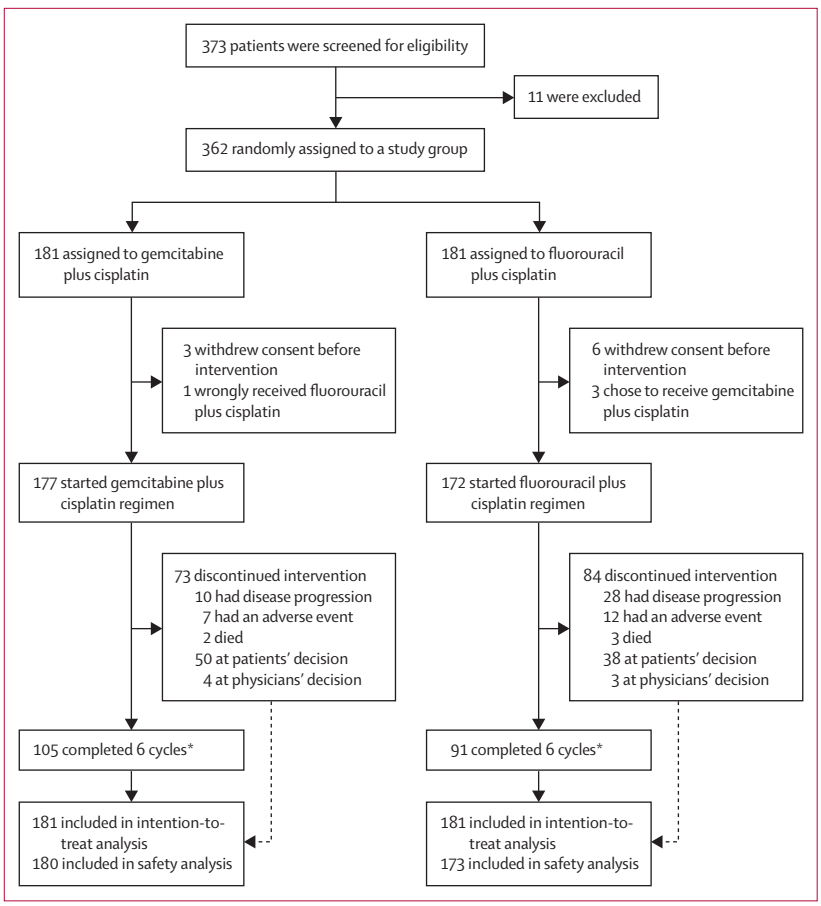

Figure 1: **Trial profile**
Cutoff date for progression-free survival was April 10, 2016. All patients randomly assigned to a study group were included in the intention-to-treat analysis according to their assigned group. All patients who received at least one dose of study treatment were included in the safety analysis according to the regimen they actually received.
*None was on treatment at the time of analysis.

We recorded post-progression survival status and treatment every 3 months. We documented adverse events at each treatment visit, follow-up visit, and at the end of the study according to the NCI-CTCAE version 3.0.

Outcomes

The independent image committee determined the primary endpoint progression-free survival. We defined progression-free survival as time from randomisation to the date of disease progression or death from any causes, whichever came first. Secondary endpoints included the proportion of patients who had a confirmed objective response (defined as a best response of complete or partial response from the initiation of treatment until disease progression or death according to the RECIST 1.1); the proportion of patients who achieved disease control (defined as objective response plus stable disease); safety profiles; and overall survival defined as the time from randomisation to the time of death. We did a planned subgroup analysis to explore the association between baseline characteristics and treatment efficacy.

Statistical analysis

The main purpose of this study was to prove the superiority of gemcitabine plus cisplatin over fluorouracil plus cisplatin regarding progression-free survival. On the basis of previous reports,[13,18–20] we assumed that the progression-free survival was 4 months in the fluorouracil group and 6 months in the gemcitabine group. With an enrolment period of 2 years and a follow-up period of 1 year, and taking into account the 5% dropout rate, we predicted that we would need a total of 362 participants with at least 198 progression-free survival events to achieve 80% power and a two-sided 5% significance-level hazard ratio (HR) of 0·67. We did not plan to do an interim analysis.

All patients randomly assigned to a group (the intention-to-treat population) were included in the primary assessment of efficacy. The safety population was defined as all patients who received at least one cycle of gemcitabine plus cisplatin or fluorouracil plus cisplatin. We included the safety population in the safety analysis. We used a log-rank test to assess the difference in progression-free survival and overall survival between the two groups. We used a Cox proportional hazards model to calculate HRs and 95% CIs. We calculated Kaplan-Meier estimates and 95% CIs at planned imaging timepoints and used them to estimate median values (with 95% CIs). Prespecified subgroups included cancer stage (recurrent or primary metastasis), sex, age (≤50 years *vs* >50 years), histology, smoking history, previous use of fluorouracil (no *vs* yes), and completion of drug cycles (≤4 *vs* 5 *vs* 6). We compared the objective response rate and disease control rate between groups using a logistic regression model. We calculated median progression-free survival and overall survival follow-up time using the reverse Kaplan-Meier method.

All statistical testing was two-sided at the nominal 5% significance level. We analysed data with SPSS version 22. This study is ongoing and is registered at ClinicalTrials.gov, number NCT01528618.

Role of the funding source

The funder of this study was involved in the audit. The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between Feb 20, 2012, and Oct 30, 2015, 362 eligible patients were randomly assigned to receive gemcitabine plus cisplatin (n=181) or fluorouracil plus cisplatin (n=181) across 22 sites in China (figure 1). 353 (98%) of 362 patients who were assigned to a group received treatment with the study drugs. One patient assigned to the gemcitabine group wrongly received fluorouracil plus cisplatin by the treating oncologist and three patients assigned to the fluorouracil group chose to

receive the gemcitabine plus cisplatin regimen. Three patients in the gemcitabine group and six patients in the fluorouracil group withdrew consent before the allocated treatment. These patients were still included in the efficacy analysis according to their assigned groups and in the safety analysis according to the regimens they were actually given (figure 1).

Baseline demographics and disease characteristics were balanced between the treatment groups (table 1). The median age was 47 years and most of the patients were non-smokers, had an ECOG PS of 1, and WHO type III histology. More than two-thirds of patients had recurrent disease and most had received induction and concurrent chemotherapy. The median cycle of treatment, relative dose intensity, and treatment cycle distribution did not differ between the two groups (appendix p 6). After documented progression, almost half of the patients (75 [41%] of 181 patients in the gemcitabine group and 86 [48%] of 181 patients in the fluorouracil group) received second-line or third-line chemotherapy (appendix p 7). The most commonly used regimen was paclitaxel-containing salvage treatment (40 [22%] of 181 patients in the gemcitabine group and 52 [29%] of 181 patients in the fluorouracil group). A minority of patients from both group received post-study ablative radiotherapy to the primary tumour or palliative radiotherapy (appendix p 8).

The data cutoff for the progression-free survival analysis was April 10, 2016, with a total of 329 events (156 in the gemcitabine group and 173 in the fluorouracil group). The median follow-up time for progression-free survival was 19·4 months (IQR 12·1–35·6). Progression-free survival by blinded independent assessment was significantly longer in the gemcitabine group (median 7·0 months [IQR 4·4–10·9; 95% CI 6·3–7·6]) than in the fluorouracil group (median 5·6 months [IQR 3·0–7·0; 95% CI 4·9–6·2]) with an unstratified HR of 0·55 (95% CI 0·44–0·68; p<0·0001; figures 2, 3). Kaplan-Meier estimates of the proportion of patients with progression-free survival were all higher in the gemcitabine (N=181) versus the fluorouracil (N=181) groups at 6 months (66% *vs* 45%), 12 months (20% *vs* 6%), and 18 months (11% *vs* 2%; figure 2). Improvement in progression-free survival was consistent across all prespecified subgroups except for the non-type-III histology and chemotherapy with five cycle subgroups (figure 3). The median follow-up time for overall survival was 22·0 months (IQR 13·0–33·5). During follow-up, 66 patients in the gemcitabine group and 95 patients in the fluorouracil group died. Median overall survival was 29·1 months (IQR 12·0–31·5; 95% CI 18·7–39·5) for gemcitabine plus cisplatin versus 20·9 months (IQR 14·6 to not reached; 95% CI 16·0–25·8) for fluorouracil plus cisplatin (HR 0·62 [95% CI 0·45–0·84]; p=0·0025; figure 2). In the gemcitabine group, 15 patients achieved complete response, 101 had partial response, 46 had stable disease, three had progressive disease, and 16 were not evaluable.

	Gemcitabine plus cisplatin (N=181)	Fluorouracil plus cisplatin (N=181)
Sex		
Male	141 (78%)	153 (85%)
Female	40 (22%)	28 (15%)
ECOG performance status		
0	59 (33%)	62 (34%)
1	122 (67%)	119 (66%)
Age (years)		
Median (IQR)	47 (39–55)	47 (41–55)
≤50	116 (64%)	110 (61%)
51–65	65 (36%)	71 (39%)
>65	5 (3%)	10 (6%)
Smoking status		
Smokers	40 (22%)	53 (29%)
Non-smokers	141 (78%)	128 (71%)
Histology*		
Non-keratinising undifferentiated (type III)	150 (83%)	150 (83%)
Non-keratinising differentiated (type II)	18 (10%)	13 (7%)
Keratinising (type I)	5 (3%)	4 (2%)
Others	8 (4%)	14 (8%)
Stage		
Primary metastases	45 (25%)	59 (33%)
Recurrence with distant metastases	131 (72%)	119 (66%)
Local recurrence	5 (3%)	3 (2%)
Metastatic organs at screening		
Lung	82 (45%)	81 (45%)
Liver	67 (37%)	76 (42%)
Bone	54 (30%)	55 (30%)
Others	11 (6%)	10 (6%)
Number of metastatic organs		
1	96 (53%)	94 (52%)
2	49 (27%)	56 (31%)
≥3	36 (20%)	31 (17%)
Previous chemotherapy		
Induction	75 (41%)	60 (33%)
Concurrent	67 (37%)	62 (34%)
Adjuvant	21 (12%)	19 (10%)
None	67 (37%)	78 (43%)
Previous chemotherapeutic agents		
Platinum	106 (59%)	91 (50%)
Fluorouracil	55 (30%)	43 (24%)
Docetaxel	19 (10%)	11 (6%)
Paclitaxel	31 (17%)	30 (17%)

Data are n (%) unless otherwise indicated. ECOG=Eastern Cooperative Oncology Group.*Histology was categorised according to the WHO Classification of Tumours.

Table 1: **Baseline demographics and disease characteristics**

In the fluorouracil group, five patients achieved complete response, 71 had partial response, 80 had stable disease, 12 had progressive disease, and 13 were not evaluable. The proportion of patients who achieved an objective

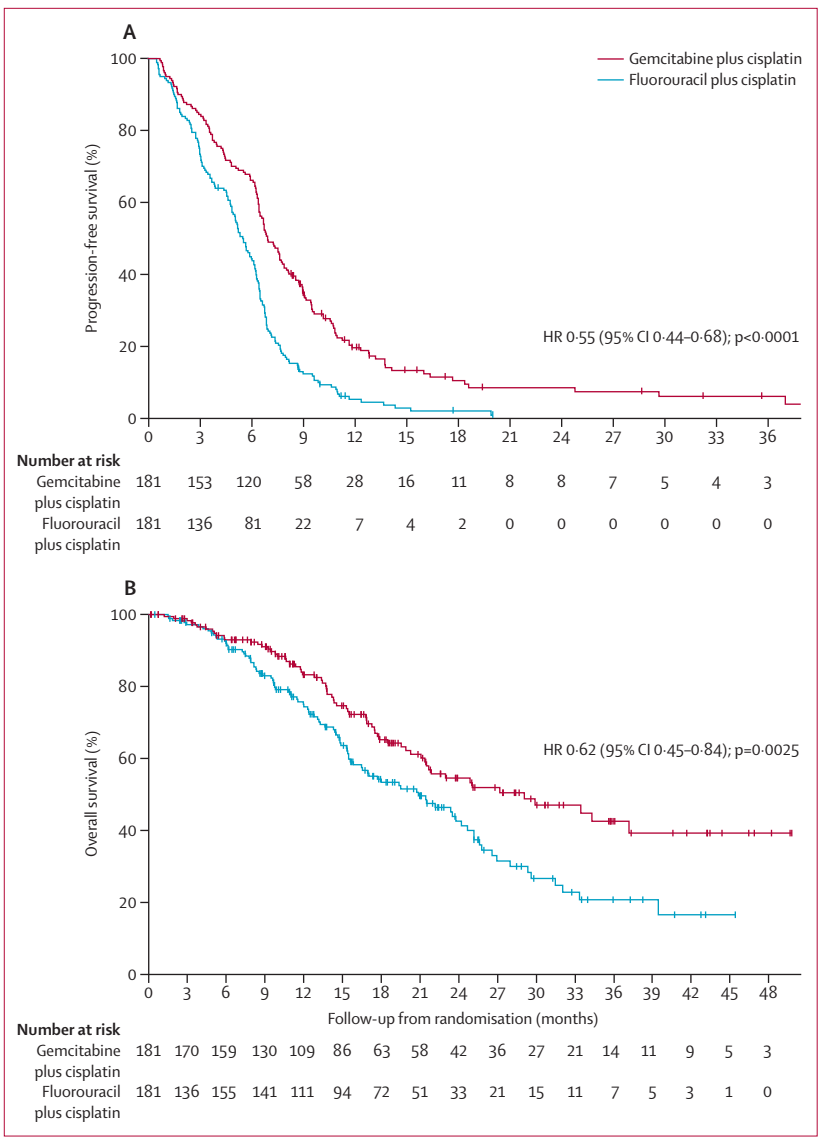

Figure 2: **Progression-free survival and overall survival in the intention-to-treat population**
(A) Progression-free survival. (B) Overall survival. HR=hazards ratio.

response was significantly higher in the gemcitabine group than in the fluorouracil group (116 [64%] *vs* 76 [42%]; relative risk 1·5 [95% CI 1·2–1·9]; p<0·0001). The disease control rate was similar for both groups (162 [90%] *vs* 156 [86%]). The efficacy of the study drugs is summarised in the appendix (p 9).

A total of 180 patients in the gemcitabine group and 173 patients in the fluorouracil group were included in the safety analysis (table 2). Overall treatment-related adverse events, including haematological and non-haematological toxic events, were similar between the gemcitabine and fluorouracil groups (table 2). Significant differences in grade 3 or higher adverse events were seen for leucopenia, neutropenia, thrombocytopenia, and mucosal inflammation (table 2). 45 (25%) patients in the gemcitabine group and 18 (10%) patients in the fluorouracil group received granulocyte-colony stimulating factor treatment in response to grade 3 or higher haematological adverse events. Serious adverse events were reported in ten (6%) of 180 patients who received gemcitabine plus cisplatin and 15 (9%) of 173 patients who received fluorouracil plus cisplatin (appendix pp 10, 11). Seven (4%) patients in the gemcitabine group had serious adverse events that were attributed to treatment (two febrile neutropenia; one leukopenia and neutropenia; one leukopenia, neutropenia, and thrombocytopenia; one leukopenia and thrombocytopenia; one pneumonia; and one vomiting and hyponatraemia). Ten (6%) patients in the fluorouracil group had treatment-related serious adverse events (one vomiting, hyponatraemia, and fainting; one syncope; two hyponatraemia; one catheter-associated infection; one renal function impairment; two leukopenia and neutropenia; one thrombocytopenia; and one catheter-associated venous thrombosis). The rate of discontinuation due to drug-related adverse events was 3% (six of 180 patients) in the gemcitabine group versus 8% (14 of 173) in the fluorouracil group. Dose reductions occurred in 18 (10%) patients in the gemcitabine group and 20 (12%) patients in the fluorouracil group. Dose delay occurred in 57 (32%) patients in the gemcitabine group and 60 (35%) in the fluorouracil group. No drug-related fatal adverse events were reported.

Discussion

Recurrent or metastatic nasopharyngeal carcinoma is highly sensitive to chemotherapy but the duration of response is short and the overall survival is poor.[12] Because of the scarcity of phase 3 clinical trials, the first-line treatment for recurrent or metastatic nasopharyngeal carcinoma is not established. In this first randomised, phase 3, head-to-head trial, the primary endpoint was reached. Compared with the traditional fluorouracil plus cisplatin regimen, gemcitabine plus cisplatin significantly prolonged progression-free survival, with consistent benefits across most prespecified subgroups including sex, age, and smoking status, histology (except for the non-type-III histology), history of chemotherapy (except for chemotherapy with five cycle subgroups), and completion of treatment cycles. Gemcitabine plus cisplatin also showed a significant improvement in the response rate and overall survival compared with fluorouracil plus cisplatin. Overall, both treatment regimens were well tolerated with predictable toxic profiles and low rates of discontinuation.

Gemcitabine is a nucleoside analogue with broad anticancer activity. Some small studies[16,18,20–22] also show that gemcitabine, whether alone or in combination with another drug, is effective in patients with nasopharyngeal carcinoma, with acceptable toxicities. Two phase 2 trials[21,23] have reported the results of gemcitabine monotherapy in patients with non-treated or pretreated,

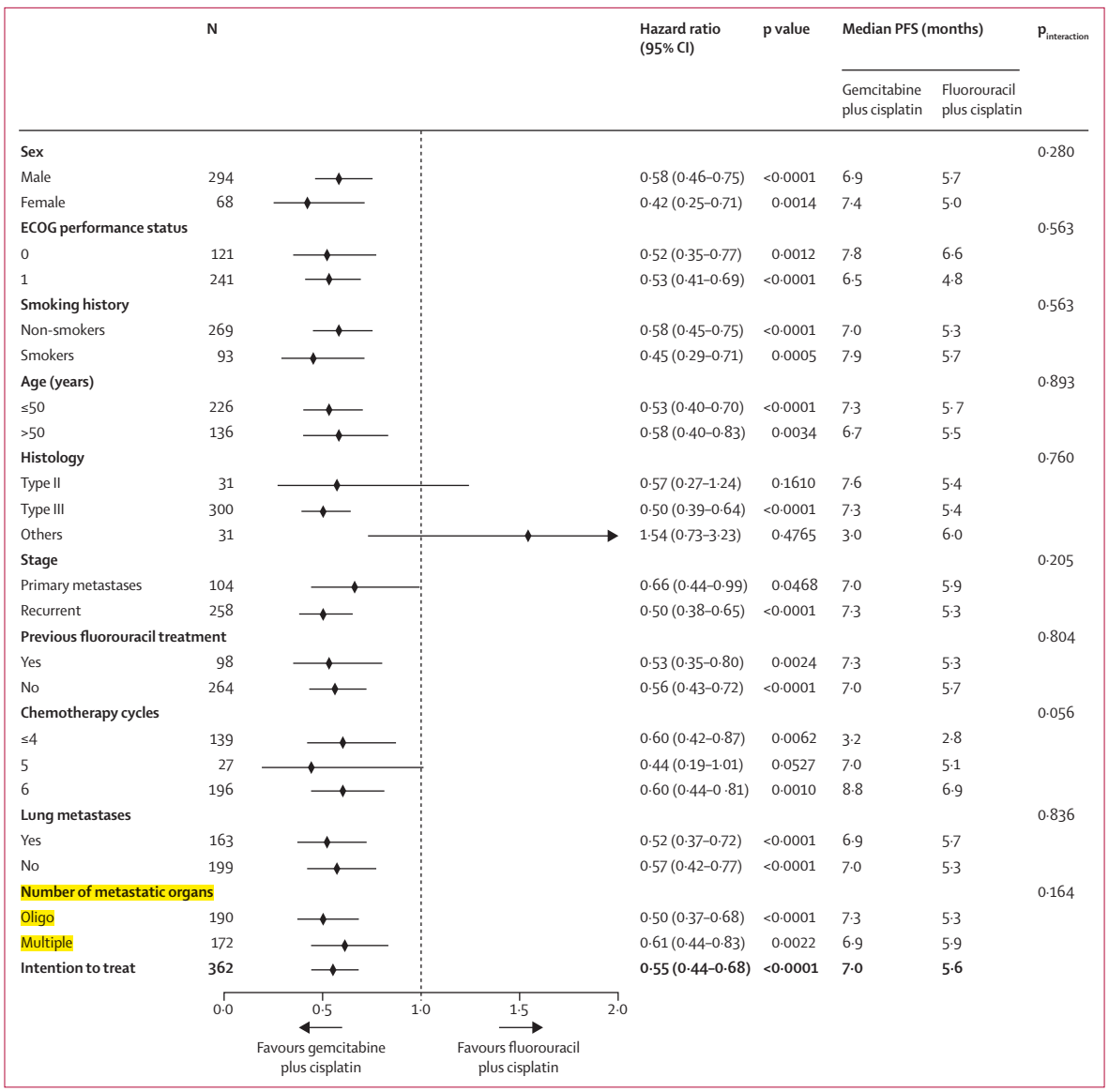

***Figure 3*: Progression-free survival by subgroup**
Effect of treatment on progression-free survival in subgroups of the intention-to-treat population defined according to prespecified factors and baseline characteristics. PFS=progression-free survival. ECOG=Eastern Cooperative Oncology Group.

recurrent or metastatic, nasopharyngeal carcinoma. In these trials, the objective response rate ranged from 28% to 48%, the median progression-free survival ranged from 3·6 to 5·1 months, and the median overall survival ranged from 7·2 to 16·0 months. Two studies[24,25] have investigated the efficacy of gemcitabine plus vinorelbin in patients with platinum-resistant advanced nasopharyngeal carcinoma. Chen and colleagues[24] reported a response rate of 37·7%, a median progression-free survival of 5·2 months, and a median overall survival of 14·1 months, whereas Wang and colleagues[25] reported a response rate of 36%, a median progression-free survival of 5·6 months, and a median overall survival of 11·9 months. A phase 2 trial[26] investigated the efficacy of gemcitabine plus S-1 (tegafur, gimeracil, and oteracil) as salvage treatment for platinum-failed nasopharyngeal carcinoma, reporting a response rate of 43%, a median progression-free survival of 5·8 months, and a median overall survival of 14·8 months. In view of the synergistic effect of gemcitabine and cisplatin in vitro, the combination of gemcitabine and cisplatin or oxaliplatin has also been investigated in three small phase 2 trials[18,20,27] for recurrent or metastatic nasopharyngeal carcinoma. Ngan and colleagues[18] reported a response rate as high as 73% and a median progression-free survival of about 10 months. However, until now, to our knowledge, no randomised trials have compared a gemcitabine-containing regimen with another drug

	Gemcitabine plus cisplatin (N=180)			Fluorouracil plus cisplatin (N=173)			p for difference in all grades	p for difference in grade 3 and 4
	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4		
Total	165 (92%)	68 (38%)	9 (5%)	162 (94%)	52 (30%)	10 (6%)	0·477	0·184
Leucopenia	134 (74%)	49 (27%)	3 (2%)	121 (70%)	15 (9%)	0	0·347	<0·0001
Neutropenia	119 (66%)	37 (21%)	4 (2%)	113 (65%)	19 (11%)	4 (2%)	0·933	0·0251
Anaemia	139 (77%)	6 (3%)	1 (1%)	125 (72%)	2 (1%)	0	0·284	0·125
Thrombocytopenia	56 (31%)	20 (11%)	4 (2%)	19 (11%)	2 (1%)	1 (1%)	<0·0001	0·0007
ALT increased	37 (21%)	3 (2%)	0	35 (20%)	1 (1%)	1 (1%)	0·940	0·687
AST increased	28 (16%)	3 (2%)	0	28 (16%)	1 (1%)	1 (1%)	0·872	0·687
Mucosal inflammation	2 (1%)	0	0	59 (34%)	22 (13%)	3 (2%)	<0·0001	<0·0001
Fatigue	20 (11%)	1 (1%)	0	22 (13%)	1 (1%)	1 (1%)	0·642	0·548
Weight loss	41 (23%)	1 (1%)	0	35 (20%)	0	0	0·561	0·516
Decreased appetite	40 (22%)	3 (2%)	0	61 (35%)	7 (4%)	0	0·0077	0·193
Nausea	41 (23%)	2 (1%)	1 (1%)	54 (31%)	3 (2%)	1 (1%)	0·076	0·665
Vomiting	18 (10%)	2 (1%)	1 (1%)	24 (14%)	1 (1%)	1 (1%)	0·264	0·687

Safety analysis included all the patients who received at least one dose of the study drug. No grade 5 drug-related adverse events occurred during the study. ALT=alanine aminotransferase. AST=aspartate aminotransferase.

Table 2: **Common drug-related adverse events**

head-to-head. These data provide the rationale for exploring the efficacy of gemcitabine plus cisplatin in the first-line treatment of recurrent metastatic nasopharyngeal carcinoma in the randomised trial design.

In this trial, we found that progression-free survival was significantly improved in the gemcitabine group, with a 45% lower risk of disease progression (or death) overall compared with the fluorouracil group. The median progression-free survival was 7·0 for gemcitabine plus cisplatin versus 5·6 months for fluorouracil plus cisplatin. At present, fluorouracil-containing regimens are widely used in the induction chemotherapy and adjuvant chemotherapy for some locally advanced nasopharyngeal carcinomas. In this study, more than two-thirds of the included patients have recurrent disease after definite radiotherapy and about a third of the patients received fluorouracil previously. However, in the subgroup analysis, the superiority of gemcitabine plus cisplatin over fluorouracil plus cisplatin with regard to progression-free survival was consistently seen in patients with various treatment backgrounds (primary metastasis *vs* recurrent after definite radiotherapy or chemo-radiotherapy; previous fluorouracil treatment *vs* no previous fluorouracil treatment). Gemcitabine plus cisplatin conferred a significant 22% improvement in objective response rate versus fluorouracil plus cisplatin. These results imply that gemcitabine has more potent and durable anticancer activities than fluorouracil does. To our knowledge, this is the first large randomised trial in metastatic or recurrent nasopharyngeal carcinoma. The results could provide strong evidence for the first-line treatment of this population.

The preliminary data suggest that gemcitabine plus cisplatin might also improve overall survival of patients with recurrent or metastatic nasopharyngeal carcinoma compared with fluorouracil plus cisplatin. We regarded progression-free survival as the most sensitive primary endpoint because it is not confounded by crossover or use of subsequent treatments. However, a 2015 meta-analysis[28] showed that progression-free survival could serve as a surrogate endpoint for overall survival in nasopharyngeal carcinoma. Notably, the post-study chemotherapy was similar between the two groups and crossover treatment was in the minority. The baseline characteristics, including sites of metastases (some retrospective studies reported that pulmonary metastasis was associated with favourable survival[29,30]), were also balanced between both groups. Therefore, the overall survival difference was mainly affected by the first-line allocation in our study. However, whether the progression-free survival benefit with gemcitabine plus cisplatin over fluorouracil plus cisplatin could be translated into overall-survival prolongation in our study population remains to be elucidated and calls for a longer follow-up.

The adverse events profiles with gemcitabine plus cisplatin and fluorouracil plus cisplatin were as expected; drug-related adverse events of leucopenia, neutropenia, and thrombocytopenia were more frequent with gemcitabine plus cisplatin, and mucositis was associated with fluorouracil plus cisplatin. A numerically higher proportion of patients in the fluorouracil group than in the gemcitabine group discontinued the study drug because of adverse events. Because of the special anatomic sites, patients with nasopharyngeal carcinoma usually have poor oral health status after radiotherapy.

Additionally, fluorouracil plus cisplatin regimens could aggravate mucosal inflammation in these patients. The deep vein catheterisation needed for fluorouracil infusion also increases the risk of catheter-associated infection and thromboembolism. All of these factors have restricted the application of fluorouracil. However, for gemcitabine plus cisplatin, the most commonly seen haematological toxicities can be more easily identified, prevented, and treated. Additionally, the administration of the gemcitabine plus cisplatin regimen is relatively simpler. The chemotherapy schedule could be given as outpatient treatment, thus reducing the costs and stress of hospital stay for the patient.

The data reported in this Article have a number of limitations. First, this study was done in an endemic area. The predominant histology was undifferentiated, non-keratinising carcinoma. Whether the results could be applied to western countries such as in Europe and North America where the incidence of nasopharyngeal carcinoma is relatively low, remains to be elucidated. Second, at the time of the present analysis, the endpoint of overall survival was not sufficiently mature to allow a full assessment. However, the preliminary results with respect to overall survival are encouraging. Third, we did not investigate the predictive role of EBV DNA in gemcitabine plus cisplatin and fluorouracil plus cisplatin regimens. It is well known that EBV infection is an important aetiological factor for the pathogenesis of nasopharyngeal carcinoma in an epidemic area. Plasma EBV DNA could be applied for detection of early disease, prediction of prognosis, and monitoring of treatment response and recurrence. However, when the trial was initiated, not all the centres did the EBV-circulating DNA assay as common practice. Therefore, the EBV DNA-level measurement was optional in our study. Additionally, the method of EBV assay was inconsistent in different centres. As such, the pooled analysis of EBV DNA was not ideal. Finally, the open-label trial design could have potentially introduced bias to some endpoints. However, this limitation has been circumvented with independent review of imaging to assess the endpoints such as progression-free survival and objective response rate. Additionally, the statisticians were blinded to patient allocation. This study is currently the largest randomised trial in metastatic or recurrent nasopharyngeal carcinoma. The results were particularly compelling with respect to clinical relevance, statistical significance (ie, remarkably lower than the 5% nominal level), data quality, and internal consistency favouring gemcitabine plus cisplatin across most endpoints and patient subgroups.

In summary, the totality of data reported in this Article shows the gemcitabine plus cisplatin regimen's improved efficacy and predictable tolerability. We believe that these data are practice changing and important for decision making when choosing a first-line treatment for patients with recurrent or metastatic nasopharyngeal carcinoma.

Contributors

LZ contributed to study design, data collection, data interpretation, and drafting of the manuscript. LZ and YH supervised the study. SH and YY contributed to data collection and management. All the authors were involved in the provision of study materials and patients, and data interpretation. All authors contributed to writing and critical review of the manuscript. LZ, YH, SH, and YY contributed equally to the Article.

Declaration of interests

LZ has received research support from Eli Lilly, Novartis, Roche, and BMS. All other authors declare no competing interests.

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