Induction chemotherapy plus concurrent chemoradiotherapy versus concurrent chemoradiotherapy alone in locoregionally advanced nasopharyngeal carcinoma: a phase 3, multicentre, randomised controlled trial

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Summary

Background The value of adding cisplatin, fluorouracil, and docetaxel (TPF) induction chemotherapy to concurrent chemoradiotherapy in locoregionally advanced nasopharyngeal carcinoma is unclear. We aimed to compare TPF induction chemotherapy plus concurrent chemoradiotherapy with concurrent chemoradiotherapy alone in a suitably powered trial.

Methods We did an open-label, phase 3, multicentre, randomised controlled trial at ten institutions in China. Patients with previously untreated, stage III–IVB (except T3-4N0) nasopharyngeal carcinoma, aged 18–59 years without severe comorbidities were enrolled. Eligible patients were randomly assigned (1:1) to receive induction chemotherapy plus concurrent chemoradiotherapy or concurrent chemoradiotherapy alone (three cycles of 100 mg/m² cisplatin every 3 weeks, concurrently with intensity-modulated radiotherapy). Induction chemotherapy was three cycles of intravenous docetaxel (60 mg/m² on day 1), intravenous cisplatin (60 mg/m² on day 1), and continuous intravenous fluorouracil (600 mg/m² per day from day 1 to day 5) every 3 weeks before concurrent chemoradiotherapy. Randomisation was by a computer-generated random number code with a block size of four, stratified by treatment centre and disease stage (III or IV). Treatment allocation was not masked. The primary endpoint was failure-free survival calculated from randomisation to locoregional failure, distant failure, or death from any cause; required sample size was 476 patients (238 per group). We did efficacy analyses in our intention-to-treat population. The follow-up is ongoing; in this report, we present the 3-year survival results and acute toxic effects. This trial is registered with ClinicalTrials.gov, number NCT01245959.

Findings Between March 1, 2011, and Aug 22, 2013, 241 patients were assigned to induction chemotherapy plus concurrent chemoradiotherapy and 239 to concurrent chemoradiotherapy alone. After a median follow-up of 45 months (IQR 38–49), 3-year failure-free survival was 80% (95% CI 75–85) in the induction chemotherapy plus concurrent chemoradiotherapy group and 72% (66–78) in the concurrent chemoradiotherapy alone group (hazard ratio 0·68, 95% CI 0·48–0·97; p=0·034). The most common grade 3 or 4 adverse events during treatment in the 239 patients in the induction chemotherapy plus concurrent chemoradiotherapy group versus the 238 patients in concurrent chemoradiotherapy alone group were neutropenia (101 [42%] *vs* 17 [7%]), leucopenia (98 [41%] *vs* 41 [17%]), and stomatitis (98 [41%] *vs* 84 [35%]).

Interpretation Addition of TPF induction chemotherapy to concurrent chemoradiotherapy significantly improved failure-free survival in locoregionally advanced nasopharyngeal carcinoma with acceptable toxicity. Long-term follow-up is required to determine long-term efficacy and toxicities.

Funding Shenzhen Main Luck Pharmaceuticals Inc, Sun Yat-sen University Clinical Research 5010 Program (2007037), National Science and Technology Pillar Program during the Twelfth Five-year Plan Period (2014BAI09B10), Health & Medical Collaborative Innovation Project of Guangzhou City (201400000001), Planned Science and Technology Project of Guangdong Province (2013B020400004), and The National Key Research and Development Program of China (2016YFC0902000).

Introduction

Nasopharyngeal carcinoma has a unique, unbalanced endemic distribution: 86 700 new cases of nasopharyngeal carcinoma were reported worldwide in 2012 with the highest incidences reported in southeast Asia, Micronesia and Polynesia, eastern Asia, and northern Africa.[1] Unlike other head and neck cancers, radiotherapy is the primary treatment modality for non-disseminated nasopharyngeal carcinoma as a result of its anatomical location and sensitivity to irradiation. More than 70% of

Lancet Oncol 2016; 17: 1509–20

Published **Online** September 26, 2016 http://dx.doi.org/10.1016/S1470-2045(16)30410-7

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Research in context

Evidence before this study

The aim of this study was to assess whether the addition of induction chemotherapy to standard concurrent chemoradiotherapy treatment provides further survival benefit in patients with locoregionally advanced nasopharyngeal carcinoma. We identified relevant studies through searches of PubMed and WHO's International Clinical Trial Registry Platform for open or closed trials with a timeframe from database inception to June 8, 2016. Search terms included "nasopharyngeal carcinoma" or "cancer" or "neoplasm", "neoadjuvant" or "induction chemotherapy", and "chemoradiotherapy". The search was limited to randomised clinical trials, with no language restrictions. So far, only three trials comparing concurrent chemoradiotherapy with induction chemotherapy followed by concurrent chemoradiotherapy have been published and the results are controversial. A phase 2 study comparing concurrent chemoradiotherapy alone with induction docetaxel and cisplatin followed by concurrent chemoradiotherapy reported improved overall survival in the induction chemotherapy plus concurrent chemoradiotherapy group. In another phase 2 trial, induction chemotherapy of cisplatin, epirubicin, and paclitaxel followed by concurrent chemoradiotherapy did not significantly improve overall survival or progression-free survival compared with concurrent chemoradiotherapy alone in stage IIB–IVB nasopharyngeal carcinoma. A randomised phase 2–3 trial comparing concurrent chemoradiotherapy alone with induction gemcitabine, carboplatin, and paclitaxel followed by concurrent chemoradiotherapy in stage III–IVB nasopharyngeal carcinoma did not record any significant improvements in survival. In three Bayesian network meta-analyses comparing concurrent chemoradiotherapy alone with induction chemotherapy plus concurrent chemoradiotherapy in nasopharyngeal carcinoma, the efficacies all seemed similar, except that induction chemotherapy plus concurrent chemoradiotherapy was associated with reduced distant metastasis. However, none of these trials used docetaxel, cisplatin, and fluorouracil (TPF), which has been shown to be an effective induction chemotherapy regimen for head and neck cancer. Besides this study (NCT01245959), several phase 3 randomised trials are also assessing the therapeutic benefits of adding different induction regimens to concurrent chemoradiotherapy (NCT00201396, NCT00705627, NCT01872962), and the results are awaited. From the aforementioned evidence, the efficacy of induction chemotherapy followed by concurrent chemoradiotherapy in patients with locoregionally advanced nasopharyngeal carcinoma remains unclear and needs evidence from large-scale, randomised controlled trials.

Added value of this study

To the best of our knowledge, this is the first phase 3 study to assess the value of adding TPF induction chemotherapy to concurrent chemoradiotherapy in nasopharyngeal carcinoma. Our results show that compared with concurrent chemoradiotherapy alone, TPF induction chemotherapy followed by concurrent chemoradiotherapy significantly increases failure-free survival, overall survival, and distant failure-free survival with acceptable toxicity.

Implications of all the available evidence

This study suggests that adding TPF induction chemotherapy to concurrent chemoradiotherapy could improve survival and reduce distant failure in locoregionally advanced nasopharyngeal carcinoma. We recommend TPF induction chemotherapy followed by concurrent chemoradiotherapy to patients with advanced nasopharyngeal carcinoma; however, long-term follow-up is required to assess the eventual efficacy and toxicity of this strategy.

cases of newly diagnosed nasopharyngeal carcinoma are classified as locoregionally advanced disease.[2] Concurrent chemoradiotherapy is now the standard treatment for locoregionally advanced nasopharyngeal carcinoma. With combined use of MRI, intensity-modulated radiotherapy, and concurrent chemoradiotherapy, locoregional control has substantially improved in nasopharyngeal carcinoma and distant metastasis is now the main source of treatment failure.[3]

Additional cycles of chemotherapy, such as the addition of adjuvant or induction chemotherapy to concurrent chemoradiotherapy, might improve distant control in patients at high risk of distant failure. However, an important concern regarding the concurrent-adjuvant approach is the low compliance to three cycles of adjuvant chemotherapy (around 60%).[4] Moreover, in our phase 3 trial,[4] the addition of adjuvant cisplatin and fluorouracil (PF) chemotherapy to concurrent chemoradiotherapy did not significantly improve treatment outcomes.[4] Compared with adjuvant chemotherapy, induction chemotherapy offers advantages of improved tolerability and early eradication of micrometastases; thus, an induction–concurrent approach might be a promising treatment strategy. However, in previous phase 3 studies that compared induction chemotherapy plus radiotherapy versus radiotherapy alone,[5–8] induction chemotherapy did not reduce distant metastasis or prolong survival; one explanation is that a truly effective induction chemotherapy regimen has not yet been identified.

Docetaxel, cisplatin, and fluorouracil (TPF) chemotherapy is an effective induction chemotherapy regimen for locoregionally advanced head and neck cancer; several large-scale phase 3 trials have confirmed the statistically significant clinical benefits of adding docetaxel to the PF induction regimen.[9–11] On the basis of encouraging results of TPF induction chemotherapy in head and neck cancer, two phase 1 studies of this induction chemotherapy in locally advanced nasopharyngeal carcinoma have been

done at our institution (Sun Yat-sen University Cancer Centre, Guangzhou, China).[12,13] Several phase 2 trials also showed promising results with manageable toxicities for TPF induction chemotherapy in nasopharyngeal carcinoma.[14–16] However, whether or not the addition of TPF induction chemotherapy to concurrent chemoradiotherapy provides any additional survival benefit in nasopharyngeal carcinoma remains unclear. Therefore, we did a multicentre, randomised controlled phase 3 trial to compare the efficacy of TPF induction chemotherapy plus concurrent chemoradiotherapy with concurrent chemoradiotherapy alone in locoregionally advanced nasopharyngeal carcinoma.

Methods

Study design and participants

This study was an open-label, multicentre, randomised controlled phase 3 trial that was done at ten hospitals in China (appendix p 3). Patients with previously untreated, non-distant metastatic, newly histologically confirmed non-keratinising stage III–IVB nasopharyngeal carcinoma (except T3–4N0; 7th Union for International Cancer Control and American Joint Committee on Cancer) were eligible. Patients had to be 18–59 years old with Karnofsky performance status scores of at least 70, and adequate bone marrow, liver, and renal function. Exclusion criteria were: treatment with palliative intent; previous malignancy; pregnancy or lactation; a history of previous radiotherapy, chemotherapy, or surgery (except diagnostic) to the primary tumour or nodes; or any severe coexisting disease. Because elderly patients generally have poor tolerance of adverse events, we excluded patients aged 60 years or older in consideration of their safety. Essential pretreatment assessments were a complete patient history, physical examination, haematology and biochemistry profiles, nasopharyngeal fibreoptic endoscopy, MRI or enhanced CT of the nasopharynx and neck (CT was indicated only in patients with contraindication to MRI), chest scan (radiograph or CT), liver scan, and bone scan. Written informed consent was obtained from all patients before enrolment. The protocol was approved by the ethics committee or institutional review board at each participating centre.

Randomisation and masking

Random assignment was done at the Clinical Trials Centre of Sun Yat-sen University Cancer Centre by a computer-generated random number code. Details of the group allocations were contained in sequentially numbered, opaque, sealed envelopes prepared by a statistician with no clinical involvement in the trial. Patients were randomly assigned in a 1:1 ratio with a block size of four (known only to the statistician). The randomisation sequence involved stratification according to treatment centre and disease stage (III or IV). Treatment allocation was unmasked. After informed consent was obtained from eligible patients, the investigators at each centre opened the envelopes sequentially, and assigned the patients to interventions.

Procedures

Eligible patients received either three cycles of TPF induction chemotherapy followed by concurrent chemoradiotherapy or concurrent chemoradiotherapy alone. In the induction chemotherapy group, TPF was administered as docetaxel 60 mg/m² intravenously every 3 weeks on days 1, 22, and 43, cisplatin 60 mg/m² intravenously every 3 weeks on days 1, 22, and 43, and fluorouracil 600 mg/m² per day as a continuous 120 h infusion on days 1–5, 22–26, and 43–47; the three cycles were administered at intervals of 3 weeks.[12,13] This group then also received concurrent chemoradiotherapy: 100 mg/m² cisplatin given intravenously every 3 weeks on days 1, 22, and 43 concurrently with radiotherapy. Patients in the concurrent chemoradiotherapy alone group only received this concurrent chemoradiotherapy regimen.

See Online for appendix

In this trial, treatment with intensity-modulated radiotherapy was mandatory, and the guidelines for intensity-modulated radiotherapy based on previous reports[3,17] are available in the appendix (pp 1–2). Gross tumour volume included the primary tumour and the enlarged lymph nodes. High-risk clinical target volume was defined as the nasopharynx gross tumour volume plus a 5–10 mm margin (2–3 mm posteriorly if adjacent to the brainstem or spinal cord) to encompass the high-risk sites of microscopic extension and the whole nasopharynx. Low-risk clinical target volume was defined as the high-risk clinical target volume plus a 5–10 mm margin (2–3 mm posteriorly if adjacent to the brainstem or spinal cord) to encompass the low-risk sites of microscopic extension, including skull base, clivus, sphenoid sinus, parapharyngeal space, pterygoid fossae, posterior parts of the nasal cavity, pterygopalatine fossae, retropharyngeal nodal regions, and the elective neck area from level IB to V. When the trial was designed, there were substantial variations in the recommended daily fraction dose for patients with nasopharyngeal carcinoma, which ranged from 2·00 Gy to 2·34 Gy.[17–20] Thus, the recommended radiotherapy dose in this study was 2·00–2·27 Gy per fraction with five daily fractions per week for 6–7 weeks; a moderate dose increase per faction to 2·35 Gy or less could be considered for some patients with early T category (T1–2) nasopharyngeal carcinoma. Cumulative doses were 66 Gy or more to the primary tumour and 50 Gy or more to the bilateral cervical lymph nodes and potential sites of local infiltration. For patients who received TPF induction chemotherapy, concurrent chemoradiotherapy was administered 3 weeks after the start of the last cycle of TPF in intervals. If only two cycles of concurrent chemotherapy were completed during the radiotherapy phase, then the third cycle of concurrent chemotherapy was given within 1 week after completion of radiotherapy.

Chemotherapy dose adjustments were allowed in cases of haematological or non-haematological toxicity. In the case of haematological toxicity, during the induction and concurrent phase, chemotherapy was withheld until the nadir values were 1500 cells per μL or higher for neutrophils and 100 000 cells per μL or higher for platelets. In the case of renal or liver toxicity, chemotherapy was withheld until adequate renal function and liver function were regained.

Dose modifications for haematological and non-haematological toxicity during induction chemotherapy or concurrent chemoradiotherapy were based on the nadir blood counts and interim toxicities of the preceding cycle. Reductions in the dose of docetaxel were planned for neutropenia, thrombocytopenia, impaired liver function, severe diarrhoea, or mucositis. Docetaxel dose had to be reduced by one level (10 mg/m²) if the patient had a second episode of febrile neutropenia, neutropenic infection, neutropenia lasting for longer than 7 days, first episode of grade 4 thrombocytopenia, aspartate aminotransferase, alanine aminotransferase, or alkaline phosphatase (more than 2·5 to 5·0 times the upper limit of normal), first episode of grade 4 diarrhoea, or second episode of grade 3 diarrhoea, or grade 4 mucositis. Modifications in the dose of cisplatin were planned for neutropenia, thrombocytopenia, nephrotoxicity, or neurotoxicity. Cisplatin dose had to be reduced by one level (10 mg/m² in the induction phase and 20 mg/m² in the concurrent phase) if the patient had grade 3 neutropenia or grade 2 thrombocytopenia (concurrent phase only), creatinine clearance of 40–60 mL/min, or grade 2 neurotoxicity. Modifications in the dose of fluorouracil were made for diarrhoea or mucositis. Fluorouracil dose had to be reduced by one level (100 mg/m²) if the patient had their first episode of grade 3–4 diarrhoea or grade 3 mucositis. Chemotherapy was stopped completely if the patient had creatinine clearance of less than 40 mL/min; aspartate aminotransferase, alanine aminotransferase, or alkaline phosphatase more than five times the upper limit of normal; second episode of grade 4 diarrhoea; or grade 3 or higher neurotoxicity or ototoxicity. Prophylactic granulocyte colony-stimulating factor was only allowed if a patient had febrile neutropenia, neutropenic infection, a delay in recovery of the absolute neutrophil count at day 28, or grade 4 neutropenia persisting for 7 days or more on the preceding cycle. Prophylactic antibiotics were administered for grade 4 neutropenia.

1 week after completion of the third cycle of induction chemotherapy and 16 weeks after radiotherapy, treatment responses were assessed with nasopharyngeal and neck MRI and flexible nasopharyngoscopy, according to the Response Evaluation Criteria in Solid Tumors (version 1.1).[21] Acute toxic effects during induction chemotherapy and concurrent chemoradiotherapy were graded according to the Common Terminology Criteria for Adverse Events (version 3.0) and late radiotherapy related toxic effects according to the Late Radiation Morbidity Scoring Criteria of the Radiation Therapy Oncology Group.[22]

Patients were assessed every 3 months during the first 3 years, and every 6 months thereafter. Whenever possible, locoregional or distant recurrences were confirmed by fine needle aspiration or biopsy. Clinical diagnosis was accepted for sites that were not accessible if classic changes were present (with or without clinical symptoms) on at least two imaging methods, including ^{18}F-fluorodeoxyglucose PET-CT, MRI, CT, chest radiograph, bone scans, and abdominal sonography; however, if imaging findings were equivocal, subsequent follow-up (eg, disease progression) would be used to ascertain the diagnosis. Each of the endpoints was assessed by the physician-in-charge. Whenever possible, salvage treatments including re-irradiation, chemotherapy, or surgery were provided in cases of documented relapse or persistent disease, in accordance with the standard practice at each centre. Patients were removed from the study if they had tumour progression or severe comorbidities during treatment, or withdrew consent at any time during the study.

Outcomes

The primary endpoint was failure-free survival, which was calculated from the date of randomisation to the date of locoregional failure, distant failure, or death from any cause, whichever occurred first. Secondary endpoints were overall survival, distant failure-free survival, locoregional failure-free survival, response rates, toxicity profile, compliance to treatment, and quality of life. Overall survival was calculated from date of randomisation to death; locoregional failure-free survival as date of randomisation to first locoregional failure; and distant failure-free survival as date of randomisation to distant failure. Complete response was defined as no unequivocal soft tissue mass in the local region and all cervical lymph nodes were less than 10 mm in the short axis. Partial response was defined as at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters. Progressive disease was defined as at least a 20% increase in the sum of diameters of target lesions (an absolute increase of at least 5 mm), or the appearance of one or more new lesions. Stable disease was defined as neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease. Late radiotherapy related toxic effects and quality of life will be presented in the long-term results of this study, but not in this report.

Statistical analysis

This study had an 80% power (two-sided α 0·05) to detect a treatment failure hazard ratio (HR) of 0·52 (two-sided log-rank test; p=0·05), assuming 3-year failure-free

survival of 88% in the induction chemotherapy plus concurrent chemoradiotherapy group and 78% in the concurrent chemoradiotherapy alone group.[3,23] We anticipated that 77 events were required in 452 patients (226 per treatment group); therefore, we needed to recruit a minimum of 238 patients per group (total 476), assuming 5% early dropout or loss to follow-up.[24]

All efficacy analyses were done in the intention-to-treat population; only patients who received their randomly assigned treatments were included in the safety analyses of adverse events. Time-to-event data were described with Kaplan-Meier curves; time-to-event intervals were compared with the log-rank test (primary analysis).[25] Missing time-to-event data (due to loss to follow-up or no event observed at the time of predefined time of primary analysis) were censored. HRs were calculated with the Cox proportional hazards model,[26] with the assumptions of proportional hazards confirmed based on Schoenfeld residuals;[27] cumulative hazard plots estimated for both groups were parallel, verifying that the assumption of proportional hazards was appropriate. Multivariate analyses with the Cox proportional hazards model were done to test the independent significance of different factors, in which all variables were entered in a single step.[26] Covariates included patient factors (ie, sex, age, and performance status), tumour factors (ie, T and N category), and chemotherapeutic intervention (ie, treatment group). A test of treatment-by-covariate interaction for the final Cox model was done to assess potential heterogeneity of treatment effects among subgroups as an exploratory analysis. Further subgroup exploratory analysis would be performed when we obtained a significant test of interaction term at the 0·1 level. Because the patients in induction chemotherapy plus concurrent chemoradiotherapy group were under treatment for 2 additional months that might inflate endpoints, time-to-event endpoints were recalculated from the end of treatment and compared between treatment groups as a post-hoc exploratory analysis. The relative dose intensity of each chemotherapy drug was calculated as the proportion of the prescribed total dose of each drug in the protocol actually received by the patients in the trial. The mean relative dose intensity of cisplatin during the concurrent phase was compared between the two groups by the Student's *t* test. Initial response rates, toxicity rates, and other categorical variables were compared by the χ^2 test (or Fisher's exact test, if indicated). Two-sided p values that were less than 0·05 were considered significant.

An independent data monitoring committee was appointed to monitor the study and make decisions regarding possible early trial closure and publication. Formal interim analysis was done on April 1, 2013, and the results were examined by the data monitoring committee. The significance threshold used for the interim analysis was defined by the O'Brien-Fleming type boundary (ie, p<0·003) for stopping the trial early.

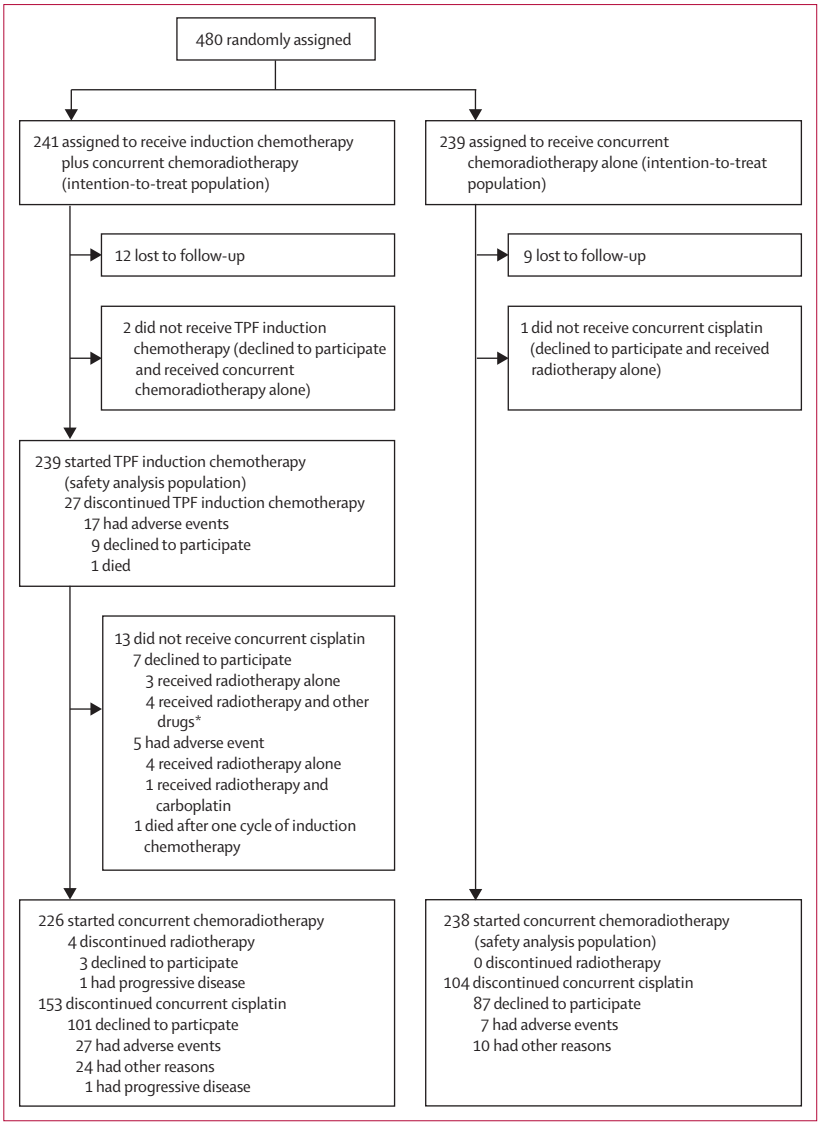

Figure 1: **Trial profile**
TPF=cisplatin, fluorouracil, and docetaxel. *Other drugs included concurrent cetuximab and nedaplatin.

All analyses were done with Stata (version 10.0). This trial is registered with ClinicalTrials.gov, number NCT01245959.

Role of the funding source

Sun Yat-sen University was involved in trial management and auditing. The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of this report. The corresponding author had full access to all the raw data in the study and had final responsibility for the decision to submit for publication.

Results

Between March 1, 2011, and Aug 22, 2013, 480 patients with locoregionally advanced nasopharyngeal carcinoma were randomly assigned to receive induction chemotherapy

	Induction chemotherapy plus concurrent chemoradiotherapy group (n=241)	Concurrent chemoradiotherapy group (n=239)
Sex		
Men	193 (80%)	174 (73%)
Women	48 (20%)	65 (27%)
Age, years	42 (36–49)	44 (39–50)
Karnofsky performance status score		
90–100	217 (90%)	211 (88%)
70–80	24 (10%)	28 (12%)
T category		
T1	15 (6%)	6 (3%)
T2	27 (11%)	19 (8%)
T3	112 (47%)	121 (51%)
T4	87 (36%)	93 (39%)
N category		
N1	97 (40%)	107 (45%)
N2	105 (44%)	106 (44%)
N3a	13 (5%)	11 (5%)
N3b	26 (11%)	15 (6%)
Disease stage		
III	129 (54%)	133 (56%)
IVA	73 (30%)	80 (33%)
IVB	39 (16%)	26 (11%)

Data are n (%) or median (IQR).

Table 1: **Baseline characteristics**

plus concurrent chemoradiotherapy (n=241) or concurrent chemoradiotherapy alone (n=239; figure 1). No patients were ineligible after randomisation. The baseline demographic and clinical characteristics of the treatment groups were well balanced (table 1). There was no significant difference in pretreatment imaging methods between the two treatment groups (appendix p 4). The last date of data collection was March 31, 2016, corresponding to 31 months of follow-up for the final patient enrolled in the study.

Overall, 239 (99%) of 241 patients in the induction chemotherapy plus concurrent chemoradiotherapy group started TPF induction chemotherapy, whereas the remaining two patients received concurrent chemoradiotherapy alone (figure 1). Of 241 patients, 212 (88%) patients completed three cycles of induction chemotherapy, 12 (5%) received two cycles, and 15 (6%) received only one cycle. The mean relative dose intensities were 93% (SD 19) for docetaxel, 93% (19) for cisplatin, and 92% (19) for fluorouracil (appendix p 10). In total, 27 (11%) of 241 patients did not complete induction chemotherapy; reasons for discontinuation were adverse events (17 [63%] of 27 patients), withdrawal of consent (nine [33%] of 27), or death (one [4%] of 27 patients; appendix p 5). The most frequent adverse event that led to discontinuation of induction TPF was hepatoxicity, accounting for six (35%) of 17 of the adverse events. Additionally, 26 (11%) of 241 patients had dose reductions, mainly due to non-haematological toxic effects. Treatment delays lasting more than 3 days occurred in 72 (30%) of 241 of patients receiving induction chemotherapy, due to adverse events and other reasons (appendix p 5) The most frequent adverse event that led to discontinuation of induction TPF was hepatoxicity, accounting for six (35%) of the 17 adverse events. The median duration from the beginning of induction chemotherapy to the beginning of radiotherapy was 66 days (IQR 62–71).

In the induction chemotherapy plus concurrent chemoradiotherapy group, 226 (94%) of 241 patients started the protocol-defined concurrent chemoradiotherapy after TPF induction chemotherapy (figure 1). Of the 15 patients who deviated from the protocol, one patient died after one cycle of induction chemotherapy and the other 14 all completed radiotherapy. Of the 226 patients who started concurrent chemoradiotherapy after induction chemotherapy, 222 patients completed radiotherapy, and four discontinued radiotherapy because they declined to participate or had disease progression, with the radiotherapy dose ranging from 25 Gy to 63 Gy. In the concurrent chemoradiotherapy alone group, 238 of 239 patients started concurrent chemoradiotherapy, one patient received radiotherapy alone, and all patients received at least 66 Gy of radiotherapy. Therefore, 236 (98%) of 241 patients in the induction chemotherapy plus concurrent chemoradiotherapy group and all 239 patients in the concurrent chemoradiotherapy group completed intensity-modulated radiotherapy as recommended by the protocol. In both treatment groups, the overall median radiotherapy dose was 70 Gy (IQR 70–70), the overall median dose per fraction was 2·19 Gy (IQR 2·12–2·26), and the overall median duration of radiotherapy was 46 days (IQR 44–49). The dose and duration of radiotherapy were similar between treatment groups (appendix p 6).

More patients in the concurrent chemoradiotherapy alone group than in the induction chemotherapy plus chemoradiotherapy group completed three cycles of cisplatin during concurrent chemoradiotherapy (134 [56%] of 239 *vs* 73 [30%] of 241; figure 1). In the induction chemotherapy plus concurrent chemoradiotherapy group, 153 patients discontinued concurrent cisplatin (138 received two cycles and 15 received only one cycle). In the concurrent chemoradiotherapy alone group, 104 patients discontinued concurrent cisplatin (102 patients had two cycles and two patients had one cycle). The most frequent reasons for discontinuation of concurrent cisplatin in in the induction chemotherapy plus concurrent chemoradiotherapy group versus the concurrent chemoradiotherapy alone group were patient refusal (101 [66%] 153 *vs* 87 [84%] of 104) and adverse events (27 [18%] 153 *vs* seven [7%] of 104; figure 1). The most frequent adverse event leading to discontinuation was

leucopenia, accounting for nine (33%) of 27 and five (71%) of seven of the adverse events in the two treatment groups, respectively. In the induction chemotherapy plus concurrent chemoradiotherapy group, 226 (94%) of 241 patients received concurrent cisplatin after induction chemotherapy. Of these 226 patients, 207 patients received at least 200 mg/m² concurrent cisplatin, whereas the other 19 patients received between 100 mg/m² and less than 200 mg/m² concurrent cisplatin. In the concurrent chemoradiotherapy alone group, 238 (100%) of 239 patients received concurrent cisplatin. Of these 238 patients, 235 patients received at least 200 mg/m² concurrent cisplatin, whereas the other three patients received between 100 mg/m² and less than 200 mg/m² concurrent cisplatin. The mean relative dose intensity for concurrent cisplatin was 71% (SD 24) in the induction chemotherapy plus concurrent chemoradiotherapy group and 84% (18) in the concurrent chemoradiotherapy alone group (p<0·0001; appendix p 10).

In total, 459 (96%) of 480 patients had regular follow-ups and physical examinations at participating centres until death or the latest scheduled assessment. At the last follow-up on March 31, 2016, the patients had been followed up for a median of 45 months (IQR 38–49); 197 (82%) of 241 patients in the induction chemotherapy plus concurrent chemoradiotherapy group and 189 (79%) of 239 patients in the concurrent chemoradiotherapy alone group were followed up for at least 3 years. Overall, 123 (26%) of 480 patients had treatment failure or died (52 [22%] of 241 patients in the induction chemotherapy plus concurrent chemoradiotherapy group and 71 [30%] of 239 in the concurrent chemoradiotherapy alone group). The proportion of patients with failure-free survival at 3 years was 80% (95% CI 75–85) in the induction chemotherapy plus concurrent chemoradiotherapy group and 72% (66–78) in the concurrent chemoradiotherapy alone alone group (HR 0·68 [95% CI 0·48–0·97], p=0·034; table 2, figure 2A).

69 patients died (26 [11%] of 241 in the induction chemotherapy plus concurrent chemoradiotherapy group *vs* 43 [18%] in the concurrent chemoradiotherapy alone group); 59 were cancer-specific deaths (21 [9%] of 241 *vs* 38 [16%] of 239) and ten patients died of non-cancer related causes (five [2%] in each group). The causes of non-cancer-related deaths included radiation-induced nasopharyngeal necrosis and massive haemorrhage (two patients in the induction chemotherapy plus concurrent chemoradiotherapy group *vs* two in the concurrent chemoradiotherapy alone group), TPF-related death (one patient *vs* no patients), cardio–cerebrovascular events (one patient *vs* two patients), pneumonia (no patients *vs* one patient), and unknown causes (one patient *vs* no patients). 3-year overall survival was significantly better in the induction chemotherapy plus concurrent chemoradiotherapy group than in the concurrent chemoradiotherapy alone group (table 2, figure 2B).

	Induction chemotherapy plus concurrent chemoradiotherapy group (n=241)	Concurrent chemoradiotherapy group (n=239)	Hazard ratio* (95% CI)	p value
Failure-free survival				
Failures	52 (22%)	71 (30%)	..	..
Proportion of patients failure-free at 3 years	80% (75–85)	72% (66–78)	0·68 (0·48–0·97)	0·034†
Overall survival				
Deaths	26 (11%)	43 (18%)	..	..
Proportion of patients alive at 3 years	92% (87–94)	86% (81–90)	0·59 (0·36–0·95)	0·029†
Distant failure-free survival				
Distant failures	27 (11%)	43 (18%)	..	..
Proportion of patients without distant failures at 3 years	90% (86–93)	83% (77–87)	0·59 (0·37–0·96)	0·031†
Locoregional failure-free survival				
Locoregional failures	20 (8%)	30 (13%)	..	..
Proportion of patients alive without locoregional failure at 3 years	92% (87–95)	89% (84–92)	0·64 (0·36–1·13)	0·12†
Response to treatment (16 weeks after the end of radiotherapy)				
Overall response	238 (99%)	239 (100%)	‡	‡
Complete response	237 (98%)	232 (97%)	‡	0·35§
Partial response	1 (<1%)	7 (3%)	‡	‡
Unassessable	3 (1%)	0 (0%)	‡	‡

Data are n (%) or % (95% CI). *Hazard ratios were calculated using the unadjusted Cox proportional-hazards model. †p values were calculated using the unadjusted log-rank test. ‡Because nasopharyngeal carcinoma is sensitive to radiotherapy and the proportion of patients achieving a complete response after concurrent chemoradiotherapy is high, we only focused on the complete response in this study. §The complete responses were compared using the unadjusted χ^2 test, thus hazard ratios and 95% CIs were not provided.

Table 2: **Survival outcomes and response to treatment**

Patients in the induction chemotherapy plus concurrent chemoradiotherapy group had significantly better 3-year distant failure-free survival than those in the concurrent chemoradiotherapy alone group (table 2, figure 2C); however, 3 year locoregional failure-free survival did not not differ significantly between the groups (table 2, figure 2D).

When the endpoints were calculated from the end of treatment rather than from randomisation as an exploratory, post-hoc analysis, the results were consistent with those calculated from randomisation (appendix pp 7, 11). In multivariate analyses, treatment group was an independent prognostic factor for overall survival and distant failure-free survival but not locoregional failure-free survival (table 3). A post-hoc exploratory analysis for covariate (eg, N1 *vs* N2–3) interaction of the treatment effect found no significant interaction (appendix pp 8, 12, 13).

1 week after the end of induction chemotherapy, 27 (11%) of the 241 patients in the induction chemotherapy plus chemoradiotherapy group had achieved complete regression considering the primary tumour and neck

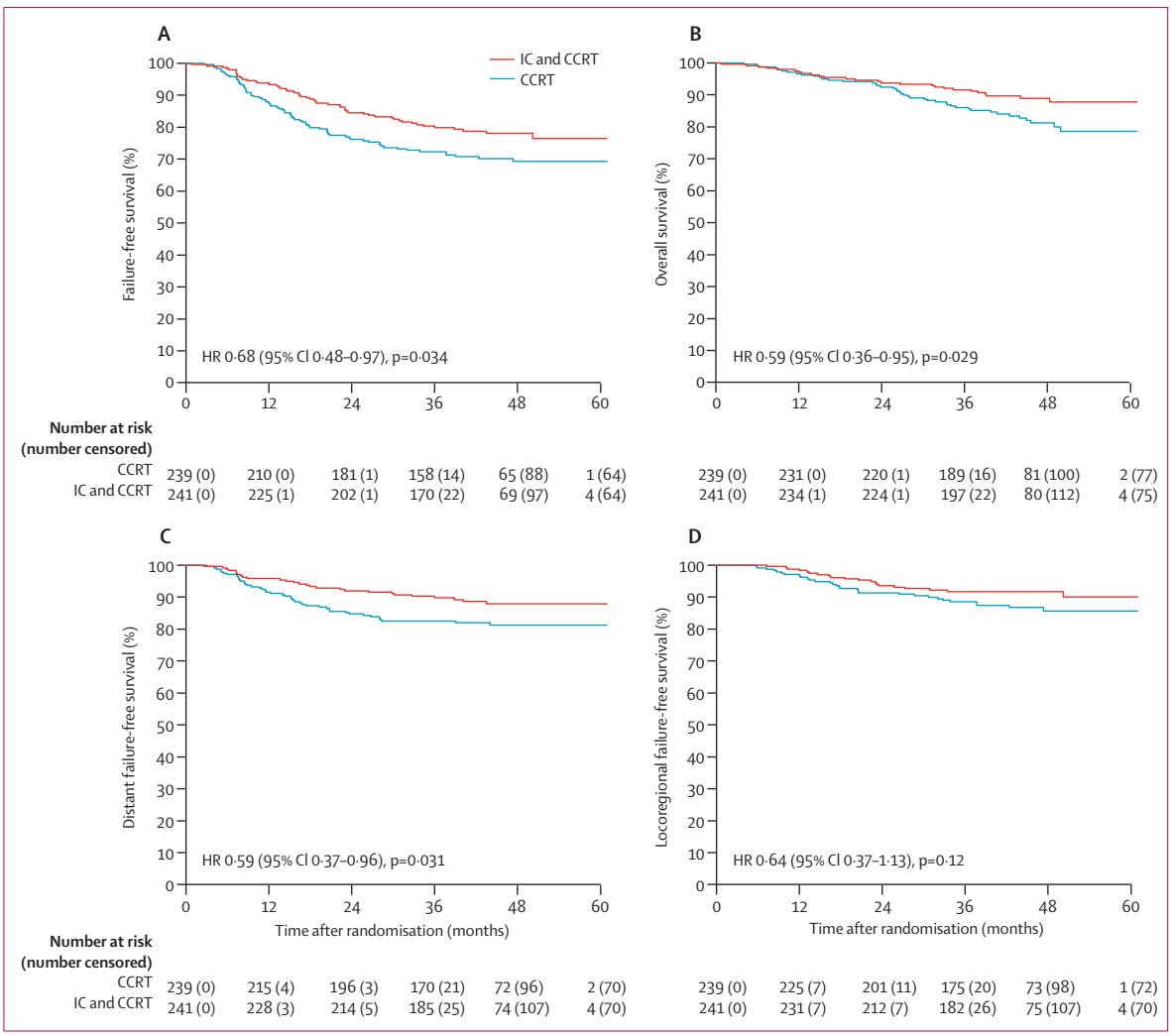

Figure 2: **Kaplan-Meier survival curves for the two treatment groups**
(A) Failure-free survival, (B) overall survival, (C) distant failure-free survival, and (D) locoregional failure-free survival, all from the start of treatment. Hazard ratios (HRs) were calculated with the unadjusted Cox proportional-hazards model; p values were calculated with the unadjusted log-rank test. CCRT=concurrent chemoradiotherapy. IC=induction chemotherapy.

together, 189 patients (78%) achieved a partial response, 21 (9%) had stable disease, four patients (2%) were non-assessable, and none developed disease progression. The proportion of patients achieving an overall response (complete and partial response) with TPF induction chemotherapy was 216 (90%) of 241. 16 weeks after the completion of radiotherapy, the proportion of patients achieving a complete response was high in both groups and did not differ between the groups (table 2).

During induction chemotherapy, 102 (43%) of the 239 patients in this group had grade 3 or 4 adverse events (appendix p 9). Grade 3 or 4 neutropenia occurred in 84 (35%) patients, followed by leucopenia (65 [27%]), diarrhoea (19 [8%]), and stomatitis (15 [6%]). One TPF-related death occurred after one cycle of induction chemotherapy; this patient did not follow the doctor's advice to receive haematological and biochemical tests after discharge from hospital and died of septic shock due to neutropenic infection and absence of timely medical care. During the entire treatment course, 174 (73%) of 239 patients in the induction chemotherapy plus concurrent chemoradiotherapy group and 128 (54%) of 238 in the concurrent chemoradiotherapy alone group had grade 3 or 4 adverse events (p<0·0001, table 4). The most common grade 3 or 4 adverse events during treatment in the 239 patients in the induction chemotherapy plus concurrent chemoradiotherapy group versus the 238 patients in concurrent chemoradiotherapy alone group were neutropenia (101 [42%] *vs* 17 [7%]), leucopenia (98 [41%] *vs* 41 [17%]), and stomatitis (98 [41%] *vs* 84 [35%]).

The induction chemotherapy plus concurrent chemoradiotherapy group had significantly higher proportions of grade 3–4 neutropenia and leucopenia than the concurrent chemoradiotherapy alone group (table 4).

The cumulative non-haematological adverse events were similar between groups, with stomatitis the most commonly reported grade 3–4 non-haematological adverse event in both groups. Only 58 (24%) of 241 patients in the induction chemotherapy plus concurrent chemoradiotherapy group received six cycles of chemotherapy with a cumulative cisplatin dose of 480 mg/m², and none of these 58 patients had grade 3–4 nephrotoxicity.

Discussion

The results of our trial show that compared with concurrent chemoradiotherapy alone, TPF induction chemotherapy followed by concurrent chemoradiotherapy could significantly increase failure-free survival, overall survival, and distant failure-free survival, but not locoregional failure-free survival, in locoregionally advanced nasopharyngeal carcinoma.

The efficacy of induction chemotherapy followed by concurrent chemoradiotherapy in nasopharyngeal carcinoma is controversial. Hui and colleagues[23] did a randomised phase 2 study comparing two cycles of induction docetaxel and cisplatin followed by concurrent chemoradiotherapy with concurrent chemoradiotherapy alone. Induction chemotherapy significantly increased 3-year overall survival, and also showed a positive effect on progression-free survival and distant control.[23] In another phase 2 trial by Fountzilas and colleagues,[28] induction chemotherapy of cisplatin, epirubicin, and paclitaxel followed by concurrent chemoradiotherapy did not significantly improve overall survival or progression-free survival compared with concurrent chemoradiotherapy alone in stage IIB–IVB nasopharyngeal carcinoma. Tan and colleagues[29] did a randomised phase 2–3 trial comparing three cycles of induction gemcitabine, carboplatin, and paclitaxel chemotherapy followed by concurrent chemoradiotherapy with concurrent chemoradiotherapy alone in patients with stage III–IVB nasopharyngeal carcinoma, and reported no significant differences in overall survival, disease-free survival, or distant failure-free survival between the two groups. The authors postulated several possible reasons for these negative results, including that the induction regimens were not effective enough, the trials were not adequately powered to detect survival differences, the doses of cisplatin during concurrent chemoradiotherapy were lower in the induction chemotherapy plus concurrent chemoradiotherapy group than in the concurrent chemoradiotherapy alone group, or induction chemotherapy might only be of benefit in some high-risk patients.[28,29]

In the present study, the treatment outcomes in the concurrent chemoradiotherapy alone group were inferior to those in similar treatment groups using intensity-modulated radiotherapy reported in some previous trials,[4,17] which might be because the patients in this trial had stage T3–4N1/N2–3M0 disease and there were more patients with stage IVB disease in this trial. Moreover, whether the endpoints were calculated from the date of randomisation or from the end of treatment, the results consistently showed that the addition of TPF induction chemotherapy to concurrent chemoradiotherapy significantly improved failure-free survival, overall survival, and distant failure-free survival in patients with locoregionally advanced nasopharyngeal carcinoma. We postulate three possible reasons for the positive results of this study. First, we used TPF as the induction regimen and this protocol has been shown to be superior to the PF regimen in head and neck cancer.[9–11] Second, in this study, the target population was patients with T3–4N1/N2–3M0 disease; patients with T3–4N0 nasopharyngeal carcinoma who have quite a low risk of distant metastasis were excluded to enhance the power of this trial to detect a survival benefit.[2,3] Third, the sample size of our trial was large enough to show the survival benefit of TPF induction

	HR (95% CI)	p value*
Overall survival		
Sex†	0·59 (0·31–1·12)	0·10
Age‡	1·00 (0·98–1·03)	0·92
Karnofsky performance status score§	1·60 (0·85–3·02)	0·14
T3 *vs* T1–2	0·56 (0·26–1·18)	0·13
T4 *vs* T1–2	1·34 (0·67–2·67)	0·41
N2 *vs* N1	2·08 (1·17–3·67)	0·012
N3 *vs* N1	2·08 (0·99–4·39)	0·054
Treatment group¶	0·54 (0·33–0·89)	0·016
Distant failure-free survival		
Sex†	0·53 (0·27–1·02)	0·059
Age‡	0·99 (0·97–1·02)	0·54
Karnofsky performance status score§	1·02 (0·50–2·07)	0·95
T3 *vs* T1–2	0·50 (0·25–1·03)	0·06
T4 *vs* T1–2	1·08 (0·56–2·08)	0·82
N2 *vs* N1	2·00 (1·11–3·60)	0·021
N3 *vs* N1	3·23 (1·62–6·43)	0·00085
Treatment group¶	0·50 (0·31–0·82)	0·0063
Locoregional failure-free survival		
Sex†	0·87 (0·44–1·71)	0·68
Age‡	1·00 (0·97–1·03)	0·89
Karnofsky performance status score§	0·71 (0·25–1·99)	0·51
T3 *vs* T1–2	1·92 (0·55–6·67)	0·30
T4 *vs* T1–2	3·02 (0·88–10·41)	0·08
N2 *vs* N1	1·30 (0·72–2·35)	0·38
N3 *vs* N1	0·53 (0·15–1·79)	0·31
Treatment group¶	0·66 (0·37–1·16)	0·15

All HRs presented in the table are adjusted for other covariates. HR=hazard ratio. *p values were calculated with an adjusted Cox proportional-hazards model. †Women versus men. ‡Age per year increase. §70–80 versus 90–100. ¶Induction chemotherapy plus concurrent chemoradiotherapy versus concurrent chemoradiotherapy alone.

Table 3: **Summary of multivariable analyses of prognostic factors**

	Induction chemotherapy plus concurrent chemoradiotherapy group (n=239)		Concurrent chemoradiotherapy group (n=238)		p value*	
	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4
Any†	132 (55%)	42 (18%)	125 (53%)	3 (1%)	0·55	<0·0001
Haematological						
Neutropenia	64 (27%)	37 (15%)	16 (7%)	1 (<1%)	<0·0001	<0·0001
Febrile neutropenia	5 (2%)	2 (1%)	0	0	0·061	0·50
Neutropenic infection	1 (<1%)	0	0	0	1·00	..
Leucopenia	86 (36%)	12 (5%)	40 (17%)	1 (<1%)	<0·0001	0·0020
Anaemia	4 (2%)	0	5 (2%)	0	0·75	..
Thrombocytopenia	5 (2%)	1 (<1%)	2 (1%)	0	0·45	1·00
Non-haematological						
Stomatitis (mucositis)	96 (40%)	2 (1%)	82 (34%)	2 (1%)	0·20	1·00
Vomiting	52 (22%)	4 (2%)	45 (19%)	0	0·44	0·12
Nausea	46 (19%)	4 (2%)	40 (17%)	0	0·49	0·12
Dry mouth	13 (5%)	..‡	13 (5%)	..‡	0·99	..
Dermatitis	8 (3%)	1 (<1%)	10 (4%)	0	0·62	1·00
Oesophagitis, dysphagia, or odynophagia	5 (2%)	0	9 (4%)	0	0·27	..
Hepatoxicity	7 (3%)	0	2 (1%)	0	0·18	..
Allergic reaction	2 (1%)	0	0	0	0·50	..

Data are n or n (%). *p values were calculated with the χ^2 test (or Fisher's exact test). †No grade 3–4 nephrotoxicity, ototoxicity, or neurotoxicity was recorded. ‡According to the Common Terminology Criteria for Adverse Events (version 3.0) dry mouth has only grade 1–3.

Table 4: **Cumulative adverse events during treatment by maximum grade per patient during treatment**

chemotherapy. Several randomised trials are also assessing the therapeutic benefits of adding different induction regimens to concurrent chemoradiotherapy (ie, NCT00201396, NCT00705627, and NCT01872962), and confirmation of the value of such strategies is awaited.

Although the dose of TPF in this study was 20% lower than that of the conventional regimen (docetaxel 60 mg/m² *vs* 75 mg/m² on day 1, cisplatin 60 mg/m² *vs* 75 mg/m² on day 1, fluorouracil 600 mg/m² *vs* 750 mg/m² per day on days 1–5),[9,10] the TPF induction chemotherapy regimen used in this study was based on two phase 1 studies done at Sun Yat-sen University Cancer Centre.[12,13] Zhang and colleagues[12] investigated the maximum tolerated dose of fluorouracil combined with docetaxel and cisplatin dose levels of 60 mg/m² each, and found that the fluorouracil maximum tolerated dose was 550 mg/m² per day on days 1–5 for patients with locoregionally advanced nasopharyngeal carcinoma. Guo and colleagues[13] did a dose-escalation study of TPF induction chemotherapy in nasopharyngeal carcinoma and recommended the following doses: 60 mg/m² docetaxel on day 1, 60 mg/m² cisplatin on day 1, and 600 mg/m² fluorouracil per day on days 1–5. During TPF induction chemotherapy in this study, 102 (43%) of 239 patients had grade 3 or 4 adverse events. The major grade 3 or 4 haematological toxicities were neutropenia (84 [35%] of 239) and leucopenia (65 [27%]), which were uncomplicated and manageable. The incidences of haematological toxicities in this study, especially neutropenia, were lower than the rates of 55–83% reported in previous studies,[9,10,14,16] probably because of the lower dose intensity of the TPF regimen used in this study. Non-haematological toxicities, such as diarrhoea, stomatitis, nausea, and vomiting, were mild and reversible in most cases. Compliance to three cycles of TPF induction chemotherapy was 88%, which is similar to other studies (ranging from 75% to 97%).[14–16] The present study suggests that this modified TPF regimen was well tolerated and produced encouraging results in Asian patients with nasopharyngeal carcinoma.

During concurrent chemoradiotherapy, only 30% of patients in the induction chemotherapy plus concurrent chemoradiotherapy group and 56% in the concurrent chemoradiotherapy alone group completed three cycles of concurrent cisplatin. Patient refusal and treatment toxicities were the most frequent reasons for discontinuation of concurrent cisplatin. Several factors contributed to the high percentage of patient refusal. Many patients were in poor health at the end of concurrent chemoradiotherapy; hypoalimentation caused by oropharyngeal mucositis and patients' fear of acute toxicities significantly decreased patient tolerance to the third cycle of concurrent chemotherapy. Nevertheless, the proportion of patients receiving at least 200 mg/m² of concurrent cisplatin was high in both groups. Previous studies have shown that the total dose of cisplatin administered during concurrent chemoradiotherapy has a substantial effect on locoregional control and overall survival, with patients who received at least 200 mg/m² of concurrent cisplatin achieving significantly better overall survival than those who received a lower dose; however, there was no evidence of improved treatment outcome

when comparing total concurrent cisplatin doses of 300 mg/m² versus 200 mg/m².[30,31] Although patients in the induction chemotherapy plus concurrent chemoradiotherapy group received somewhat lower cisplatin doses during concurrent chemoradiotherapy than those in the concurent chemoradiation alone group, the proportion of patients achieving a complete response after concurrent chemoradiotherapy was similar between the two treatment groups. We propose two possible contributory factors. First, nasopharyngeal carcinoma is sensitive to radiotherapy and the proportion of patients achieving a complete response with radiotherapy alone is high,[32,33] and 236 (98%) of 241 patients in the induction chemotherapy plus concurrent chemoradiotherapy group completed radical intensity-modulated radiotherapy. Second, TPF induction chemotherapy might compensate for the negative effects of quite low-dose concurrent cisplatin on survival.

This study has several limitations. First, we only used TNM stage to measure disease stage and select eligible participants, and did not include non-anatomical prognostic biomarkers, such as plasma Epstein-Barr virus DNA load.[34] However, since quantitative plasma Epstein-Barr virus DNA assays done at different clinical laboratories could yield large variability in copy number without harmonisation and the problem of assay standardisation remained unsolved before the trial started, plasma Epstein-Barr virus DNA load was not included as a prognostic factor in this study. Second, this study excluded patients aged 60 years or older in consideration of their safety; therefore these results do not have generalisability to elderly patients, although the effect is limited due to the small number (about 10%) of such patients.[3] Third, when we designed the trial, there was no consensus on the optimal dose fractionation of intensity-modulated radiotherapy in nasopharyngeal carcinoma.[17–20] Thus, we used the daily fraction of 2·00–2·27 Gy, and a moderate dose increase per fraction to 2·35 Gy or less could be considered for some patients with T1–2 nasopharyngeal carcinoma; the optimal dose schedule of intensity-modulated radiotherapy in nasopharyngeal carcinoma still needs further evaluation. Fourth, in this study, we used nasopharyngeal and neck MRI and flexible nasopharyngoscopy to assess the treatment response at 16 weeks after intensity-modulated radiotherapy. However, postradiotherapy oedema, inflammation, and fibrosis might interfere with the response assessment; thus, if equivocal findings were found, subsequent follow-up would be used to determine the final response. Finally, we only reported the 3-year survival results and acute toxicities in this study, and need to follow up patients at 5 years when more events become available to fully assess overall survival and late toxic effects.

In conclusion, this study suggests that, compared with concurrent chemoradiotherapy alone, induction chemotherapy based on TPF plus concurrent chemoradiotherapy could improve failure-free survival, overall survival, and distant failure-free survival in locoregionally advanced nasopharyngeal carcinoma with an acceptable toxicity profile. However, long-term follow-up is needed to assess the eventual efficacy and toxicity of TPF induction chemotherapy.

Contributors

JM was responsible for conception and design, supervised the project, quality assessment, review, and approval of the manuscript. YiS, W-FL, N-YC, NZ, G-QH, F-YX, YaS, X-ZC, J-GL, X-DZ, C-SH, X-YX, and LC contributed to design of clinical trial, writing of the protocol, recruitment and treatment of patients, data and trial management, data analysis and interpretation, and writing and final approval of the report. Y-YC, W-HH, LG, and H-YM were involved in design of clinical trial, recruitment and treatment of patients, data and trial management, and review of the report. Y-PM, RS, PA, S-BL, G-XL, B-MZ, X-LF, X-CG, LLi, C-YS, and J-YX participated in recruitment and treatment of patients, data and trial management, and report preparation. YG and Y-MC were responsible for statistical analysis and interpretation, and toxicity and data review. FZ, LLin, and L-LT contributed to patient accrual and writing or reviewing of the completed report. M-ZL was involved in trial management and toxicity review. All authors have read and approved the final draft.

Declaration of interests

We declare no competing interests.

Acknowledgments

This is an investigator-initiated study. This study is mainly funded by the Shenzhen Main Luck Pharmaceuticals Inc, Sun Yat-sen University Clinical Research 5010 Program (no. 2007037), the National Science & Technology Pillar Program during the Twelfth Five-year Plan Period (2014BAI09B10), the Health & Medical Collaborative Innovation Project of Guangzhou City (201400000001), the Planned Science and Technology Project of Guangdong Province (no. 2013B020400004), and The National Key Research and Development Program of China (2016YFC0902000). Shenzhen Main Luck Pharmaceuticals Inc provided free drugs (docetaxel, cisplatin, and fluorouracil) for this study. We thank the patients who participated in this study, their families, and the medical, nursing, and research staff at the study centres. We are grateful to Xiao-Qing Hu, Yuan-Yuan Li, and Hui-Xia Feng (Department of Radiation Oncology, Sun Yat-sen University Cancer Centre), and Yan Xu (Department of Science and Technology, Zhejiang Cancer Hospital) for assistance with the data management and logistic support. We thank the Department of National Clinical Study Centre for Anticancer Drugs, Sun Yat-sen University Cancer Centre, for trial monitoring, data management, and statistical analysis. We also thank Pierre Blanchard (Department of Radiation Oncology and Meta-analysis Unit, Department of Biostatistics and Epidemiology, Gustave Roussy Cancer Center, France) for their help with statistics.

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