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Chemotherapy regimens containing taxanes or fluorouracil in nasopharyngeal carcinoma: Which better?

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ABSTRACT

Objectives: The efficacy of various chemotherapy regimens in nasopharyngeal carcinoma (NPC) remains under debate. We compared the efficacy and toxicity of a taxane-based regimen and regimen including fluorouracil in NPC.

Materials and methods: Eight-hundred and six patients with stage II-IVB NPC from four institutions in China were pair-matched (1:1 ratio) to the cisplatin plus fluorouracil (PF) group or cisplatin plus taxanes (TP) group using eight clinical factors. Overall survival (OS), disease-free survival (DFS), locoregional relapse-free survival (LRRFS) and distant metastasis-free survival (DMFS) were assessed using the Kaplan-Meier method and Cox regression model. Toxicities were assessed in all patients.

Results: Three-year DFS was significantly better in the TP group than PF group (82.5% vs. 72.7%, $P = 0.002$), with no significant difference in OS, LRRFS or DMFS. TP led to significantly better DFS compared to PF in the subgroups advanced stage NPC, patients aged ≤45-years-old and female patients. In multivariate analysis, chemotherapy regimen was an independent prognostic factor for DFS [hazard ratio, 0.591, 95% CI 0.444–0.786, $P = 0.000$]. Grade 3–4 leukopenia, neutropenia and anemia were significantly more common in the TP group; grade 3–4 mucositis, vomiting, vasculitis and diarrhea were more common in the PF group.

Conclusion: Taxane-based regimens have a higher efficacy in NPC than regimens including fluorouracil, especially in patients with advanced stage, patients aged ≤ 45-years-old and female patients.

Background

Unlike other head and neck carcinomas, nasopharyngeal carcinoma (NPC) has a unique regional distribution [1]. NPC is disproportionally common in southern China, with incidence of up to 30 cases per 100,000 in Guangxi and Guangdong provinces [2,3].

A high rate of distant metastasis is the main reason for the poor prognosis of NPC [4]. Chemotherapy remains the major treatment for the disease and significantly improves survival outcomes [5]. The classic combination of cisplatin and 5-fluorouracil (PF) is routinely adopted for NPC [6]. Third-generation cytotoxic agents, such as the taxanes paclitaxel (PTX) and docetaxel (TXT), are also frequently combined with cisplatin. These combined chemotherapy regimens are considered to be effective in clinical practice as they exert a radiosensitizing effect [7].

However, although the taxanes plus cisplatin (TP regimen) and fluorouracil plus cisplatin (PF regimen) may both improve treatment outcomes, there have been few direct comparisons of taxanes and fluorouracil-based chemotherapy regimens in NPC. Moreover, some clinical trials have reported inconsistent survival and toxicity outcomes for different regimens. A trial by Johnson et al. found that the PF regimen led to a better complete response (CR) in NPC compared to TP regimen [8]. However, a Turkish study reported no significant difference in median OS between the TP and PF regimens [9]. A meta-analysis indicated the TP regimen is safer and more effective than the PF regimen [10]. Additionally, Xu et al. reported the PF and TP regimens led to similar progression free survival (77.3% vs. 71.1%, $P > 0.05$) and OS (81.6% vs. 83.7%, $P > 0.05$) in locally advanced NPC [11]. To complicate matters, the efficacy of different chemotherapy regimens may vary in different subgroups of patients with NPC, and the optimal

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dose intensities and regimens have not yet been established for each regimen.

Thus, we conducted a pair-matched analysis to compare the efficacy and safety of the TP regimen and PF regimen in order further refine treatment strategy selection for patients with NPC.

Materials and methods

Patient selection

We retrospectively assessed all patients with NPC treated at the Affiliated Hospital of Guilin Medical University, Wuzhou Red Cross Hospital, Nanxi Shan Hospital and Lingshan People's Hospital between January 2008 and January 2013. Selection criteria were: pathological diagnosis of NPC; aged between 18 and 70-years-old; stage II-IVB NPC according to the seventh edition of the AJCC/UICC staging system; Eastern Cooperative Oncology Group (ECOG) performance status < 3; no prior chemotherapy or radiation therapy, and no distant metastasis before treatment. The exclusion criteria were: second primary malignancy, pregnancy or lactation, not receiving chemotherapy regimens containing taxanes or fluorouracil, allergy to platinum-based drugs and/or taxanes, lung or heart dysfunction, and a history of hepatitis or nephritis.

As the baseline characteristics of the patients who received the TP and PF regimens were significantly different, patients were selected using a pair-matching method [12] to reduce possible biases to a minimum in four institutions. Pairs were matched according to following factors in a descending hierarchy: T category (T1 vs. T2 vs. T3 vs. T4), N category (N0 vs. N1 vs. N2 vs. N3), clinical stage (II vs. III vs. IVA vs. IVB), RT regimen (two-dimensional radiation treatment (RT) vs. three-dimensional conformal RT vs. intensity-modulated radiation therapy), treatment mode (induction chemotherapy (IC) + concurrent chemoradiotherapy (CCRT) vs. IC + RT vs. CCRT vs. CCRT + adjuvant chemotherapy (AC)), age (≤45 vs. > 45 years), sex (male vs. female), and WHO histology (I vs. II vs. III). Patients who received TP regimen were matched in a 1:1 ratio with patients treated with PF regimen. If an exact matched patient was unavailable, the matching limitations were extended until the right patient was found. The matched pairs were allowed to differ in maximum three of these eight factors.

All patients written informed consent before they began treatment. The protocol was conducted in accordance with the Good Clinical Practice Guideline and approved by the Research Ethics Committees of the four institutions.

Radiation therapy and chemotherapy

All patients received definitive radiotherapy based on two-dimensional RT (2D-CRT), three-dimensional conformal RT (3D-CRT) or intensity-modulated radiation therapy (IMRT). Irradiation was administered at 2.0–2.3 Gy per fraction daily from Monday to Friday for 6–7 weeks, the cumulative radiation dose was 68 Gy or greater to the primary gross tumor volume, 67–70 Gy to the involved neck area and 54 Gy to the potential sites of local infiltration.

Patients received either the PF regimen, which consisted of 5-FU (600–800 mg/m^2, on days 1–5) plus cisplatin (25 mg/m^2, on days 1–3) or the TP regimen, which consisted of paclitaxel (175 mg/m^2, on day 1) or docetaxel (75 mg/m^2, on day 1) plus cisplatin (25 mg/m^2, on days 1–3). Patients receiving induction chemotherapy received three cycles of the PF or TP regimen, with radiotherapy administered 3 weeks after the last cycle of chemotherapy. Patients receiving concurrent chemoradiotherapy received 2 cycles of PF or TP concurrently with radiotherapy. Patients receiving adjuvant chemotherapy received three cycles of adjuvant TP or PF one month after completing radiotherapy. Each cycle interval was 21 days.

Follow up and evaluation

The median follow-up period was 49 months (range, 1–99 months), follow-up duration was measured from the first day of therapy to day of last examination or death. Patients were evaluated every 3 months during the first 3 years, every 6 months in the fourth and fifth years, and annually thereafter. Tumor response rate was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0. Toxicities were graded from 0 to 4 using to the National Cancer Institute Common Toxicity Criteria Version 3.0. RT-related toxicities were recorded using the Radiation Morbidity Scoring Criteria of the Radiation Therapy Oncology Group.

The primary end-point of the study was overall survival (OS), the secondary end-points were disease-free survival (DFS), locoregional relapse-free survival (LRRFS), distant metastasis-free survival (DMFS) and treatment-related toxicity. OS was calculated from the time of registration to death from any cause; DFS, to treatment failure or death from any case; LRRFS to first locoregional relapse or last follow-up; and DMFS to first detection of metastasis.

Statistical analysis

Differences in proportions between groups were assessed using the x^2 test. The Kaplan-Meier method was used to estimate actuarial rates, survival curves were compared using the log-rank test. Multivariate analyses were performed using the Cox proportional hazard model to identify potentially independent prognostic factors after adjusting for age, gender, T category, N category and chemotherapy regimen. An adjusted Cox proportional hazard model was used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs). All statistical analyses were performed using Stata 10 (StataCorp LP); all *P*-values are two-tailed, $P < 0.05$ was considered significant.

Results

Patient characteristics

A total of 1721 patients with NPC of stage II-IVB were selected in our study between January 2008 and January 2013, 325 patients were excluded because lost to follow up, 98 patient were exclude due to the lack of information, 364 patients were exclude after applying the inclusion and exclusion criteria, resulting in 934 patients, following matching, 806 pair-matched patients (403 in the PF group and 403 in the TP group; Table 1) were retrospectively analyzed. Of the 806 pair-matched patients, 607 (75.3%) were male and 199 (24.7%) were female; 778 (96.5%) had WHO Type III NPC; 341 (42.3%) received 2D-RT, 50 (6.2%) received 3D-CRT and 415 (51.5%) received IMRT; 58 (7.2%) had AJCC stage II, 443 (55.3%) had AJCC stage III, 227 (28.1%) had AJCC stage IVA and 78 (9.7%) had AJCC stage IVB NPC.

IC followed by CCRT was delivered to 378 (46.9%) patients, CCRT to 232 (23.8%) patients, and CCRT plus AC to 161 (20.0%) patients. There were no significant differences between the baseline characteristics of the PF group and TP group (Table 1).

Treatment administration

The treatment modes in the 4 institutions were administrated according to the NCCN (National Comprehensive Cancer Network) guidelines. All 806 pair-matched patients (100%) received curative intent radiotherapy. Overall, 251 (62%) patients in the TP group and 264 (66%) in the PF group completed three or more cycles of chemotherapy; 137 (34%) vs. 129 (32%) completed two cycles of chemotherapy; and 15 (4%) vs. 10 (2%) completed one cycle of chemotherapy due to grade 4 neutropenia or serious gastrointestinal adverse. In the TP group, 299 received paclitaxel plus cisplatin and 104 received docetaxel plus cisplatin. The median total doses of paclitaxel,

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