RESEARCH COMMUNICATION

Concurrent Weekly Docetaxel Chemotherapy in Combination with Radiotherapy for Stage III and IVA-B Nasopharyngeal Carcinoma

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Abstract

Background and Purpose: Cisplatin is the most common chemotherapeutic agent for loco-regionally advanced nasopharyngeal carcinoma (NPC); however, toxicity is a limiting factor for some patients. We retrospectively compared the efficacy and toxicity of weekly docetaxel-based and cisplatin-based concurrent chemoradiotherapy in loco-regionally advanced NPC. Methods and Materials: Eighty-four patients with Stage III and IVA-B NPCs, treated between 2007 and 2008, were retrospectively analyzed. Thirty received weekly docetaxel-based concurrent chemotherapy, and 43 were given weekly cisplatin-based concurrent chemotherapy. Radiotherapy was administered using a conventional technique (seven weeks, 2.0 Gy per fraction, total dose 70-74 Gy) with 6-8 Gy boosts for some patients with locally advanced disease. Results: Median follow-up time was 42.3 months (range, 8.6-50.8 months). There were no significant differences in the 3-year loco-regional failure-free survival (85.6% vs. 92.3%; p=0.264), distant failure-free survival (87.0% vs. 92.5%; p=0.171), progression-free survival (85.7% vs. 88.4%; p=0.411) or overall survival (86.5% vs. 92.5%, p=0.298) of patients treated concurrently with docetaxel or cisplatin. Severe toxicity was not common in either group. Conclusions: Weekly docetaxel-based concurrent chemoradiotherapy is potentially effective and has a tolerable toxicity; however, further investigations are required to determine if docetaxel is superior to cisplatin for advanced stage NPC.

Keywords: Cisplatin - chemoradiotherapy - nasopharyngeal carcinoma - docetaxel

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Introduction

Nasopharyngeal carcinoma (NPC) is particularly common in the Cantonese population of China, especially in Guangdong province. Undifferentiated World Health Organization (WHO) type III disease accounts for more than 95% of endemic NPC, which is very sensitive to radiation. Although early-stage NPC can be well controlled using radiotherapy alone, advanced-staged disease remains difficult to treat due to the high rate of relapse and metastases (Cao et al., 2011). Randomized prospective studies and meta-analysis have confirmed that the addition of concurrent chemotherapy to radiotherapy improves local control and overall survival in locoregionally advanced NPC, compared to radiotherapy alone (Al-Sarraf et al., 1998; Lin et al., 2003; Langendijk et al., 2004; Chan et al., 2005; Lee et al., 2005; Wee et al., 2005; Baujat et al., 2006).

Though cisplatin is the most commonly used clinical chemotherapeutic agent for NPC, cisplatin toxicity is a limiting factor for some patients, and there is little research on the optimal chemotherapy drug and schedule for concurrent radiotherapy in NPC. Based on a series of preclinical research data, taxane-based chemotherapeutic agents, including docetaxel and paclitaxel, have demonstrated beneficial effects as radiosensitizing drugs, and have attracted significant interest for combination chemoradiotherapy (Tishler et al., 1992; Wahl et al., 1996; Tishler et al., 2002). Phase I/II clinical trials proved that concurrent docetaxel chemotherapy and radiation were effective in squamous cell carcinoma of the head and neck (SCCHN) (Tishler et al., 2002; Calais, et al., 2004; Tishler et al., 2006; Biete et al., 2007; Fukada et al., 2010), however, the benefit of concurrent docetaxel radiochemotherapy in NPC has not been investigated. Promising results have been reported for other taxanes in concurrent chemotherapy regimes, as the outcome of advanced NPC patients receiving pacitaxel was encouraging (Chen, et al., 2004; Chen et al., 2007; Hu et al., 2009); however, it is still not clear whether there

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are differences in the toxicity and treatment outcome of docetaxel-based and cisplatin-based concurrent chemotherapy regimes in NPC.

From January 2007 onwards, some Stage III and IVA-B NPC patients received concurrent docetaxel-based chemoradiotherapy at our institution. In this retrospective study, we compared the toxicity and treatment outcomes of docetaxel-based and cisplatin-based concurrent chemotherapy in patients with advanced NPC.

Materials and Methods

Patients and methods

Between January 2007 and December 2008, patients diagnosed and treated with advanced NPC at Cancer Center, First People's Hospital of Foshan Affiliated to Sun Yat-sen University were included in this retrospective study. All patients had biopsy proven NPC, according to the WHO (2005) criteria, before treatment began. Patients presenting with Stage III (T3N0-2M0, T1-3N2M0), Stage IVA (T4N0-2M0) and Stage IVB (T1-3N3M0) NPC, based on the criteria of the American Joint Committee on Cancer/International Union against Cancer (AJCC/UICC, 6th, 2002) received concurrent chemotherapy. Staging workup included a complete physical examination, fiber-optic nasopharyngoscopy, nasopharyngeal and cervical region magnetic resonance imaging (MRI), chest X-ray, liver ultrasound and bone scan. All patients had adequate pretreatment organ function and hematological reserves with an absolute neutrophil count (ANC) $\geq 1.8\times10^9$/L, platelet count $\geq 100\times10^9$/L, creatinine clearance (CrCl) ≥40 ml/min, and alanine aminotransferase (ALT) and alkaline phosphatase (ALP) levels within normal limits (30 unit and 115 unit, respectively).

External beam radiotherapy was delivered using a 6 MV linear accelerator (Varian C600, USA). The plan design included two standard laterally opposed fields: a supraclavicular field and a single anterior field with midline blocking in the supraclavicular field to shield the spinal cord. Radiotherapy was delivered at a dose of 2 Gy per day, five times per week for 7 weeks. The planned dose was 70-74 Gy to the primary tumor, 64-70 Gy to the regional metastatic nodes, and 50-54 Gy to the uninvolved nodes. Some patients with T3/T4 tumors involving the skull base or with intracranial extension were given a 2DRT boost, using two small lateral fields to encompass the damaged skull base and part of the primary tumor, with a planned boost dose of 6-8 Gy. The dose to the spinal cord was limited to below 45 Gy.

Patients received concurrent weekly chemotherapy with radiotherapy over 6-7 planned cycles. Cisplatin (30 mg/m^2) or docetaxel (30 mg/m^2) were delivered via intravenous infusion administered 1 hour before radiotherapy. Premedication for cisplatin included ondansetron (8 mg intravenously) and vigorous hydration to maintain a urine output >100-150 ml/h. Premedication for docetaxel included dexamethasone (10 mg intravenously), ondansetron (8 mg intravenously) or gelarsichone (4 mg intravenously), and ranitidine (50 mg) or omeprazole (20 mg intravenously) 30 min before docetaxel infusion. Treatment toxicities were graded according to the National Cancer Institute Common Toxicity Criteria version 3.0.

Follow-up

Patient follow-up data was analyzed up to and including September 30th, 2011. Patients were assessed every 2-3 months for the first year, every 3-6 months for the next two years, and then every six months or yearly thereafter. Each follow-up visit included a routine physical examination, MRI of the head and neck, and fiber-optic endoscopy if indicated. A chest X-ray, abdomen and pelvic ultrasound, and total body bone scan was also performed every 3-6 months or earlier, according to the discretion of the treating physician.

Statistical analyses

Locoregional failure-free survival (LFS) and distant failure-free survival (DFS) were defined as the date of diagnosis to the date of the first local or remote failure, respectively. Progression-free survival (PFS) was defined as the interval from the date of diagnosis to the date of disease progression, relapse or death from any cause. Overall survival (OS) was defined as the interval between the date of diagnosis and to the date of death from any

Table 1. Characteristics of the NPC Patients

Characteristic	Concurrent docetaxel Number (%)	Concurrent cisplatin Number (%)	P-value
Sex			0.657
Male	23(76.7%)	39(72.2%)	
Female	7(23.3%)	15(27.8%)	
Age			0.51
Mean	50	48	
Range	13-78	25-72	
Staging method			
Head and neck MR	30 (100%)	54(100%)	
Pathology			0.93
Differentiated	1(3.3%)	2(2.4%)	
Undifferentiated	29 (96.7%)	52(96.3%)	
T Stage			0.038
T1	1(3.3%)	0(0%)	
T2	8(26.7%)	4(7.4%)	
T3	9(30.0%)	26(48.1%)	
T4	12(40.0%)	24(44.4%)	
N Stage			0.336
N0	2(6.7%)	5(9.3%)	
N1	9(30.0%)	25(46.3%)	
N2	16(53.3%)	22(40.7%)	
N3	3(10.0%)	2 (3.7%)	
TNM			0.216
III	13(43.3%)	31(57.4%)	
IVA-B	17(56.7%)	23(42.6%)	
Chemotherapy Weekly dose			
Mean(mg)	48.87	50.22	
Std. (mg)	6.388	6.008	
Cycles			0.207
2-4	4(13.3%)	11(20.4%)	
5-7	26(86.7%)	43(79.6%)	
Radiotherapy			
Total dose (cGy): Median Nasopharynx	7400	7800	0.032
Cervical involved nodes	6600	6600	0.341
Uninvolved nodes	5000	5000	0.635

*6th AJCC/UICC Staging system (2002)

Table 2. Incidence of Each Grade of Chemoradiotherapy-related Toxicity in Stage III and IVA-B NPC Patients Treated with Concurrent Radiotherapy and Docetaxel (n = 30) or with Concurrent Radiotherapy and Cisplatin (n = 54)

	Concurrent docetaxel (n)					Concurrent cisplatin (n)					P-value
Toxicity	0	1	2	3	4	0	1	2	3	4	
Hemoglobin	18	11	1	0	0	8	41	5	0	0	0.000
Neutrophils	23	7	0	0	0	30	16	4	3	1	0.193
Platelets	30	0	0	0	0	47	6	0	1	0	0.120
Neutropenic fever	29	1	0	0	0	49	3	1	0	0	0.664
WBC	12	12	4	2	0	4	15	25	10	0	0.000
Vomiting	28	1	1	0	0	3	28	23	0	0	0.000
Hepatic	25	1	3	1	0	42	9	3	0	0	0.152
Creatinine	29	1	0	0	0	50	4	0	0	0	0.450
Mucotisis	0	2	20	8	0	0	6	44	3	1	0.044

WBC, white blood cell

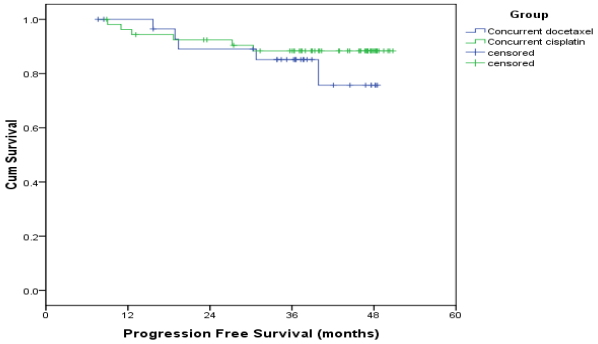

Figure 1. Progression-free Survival

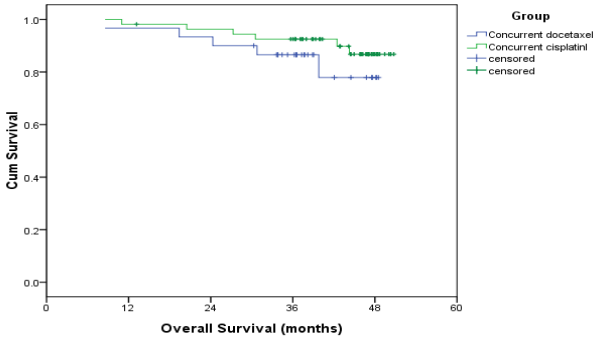

Figure 2. Overall Survival

cause. All survival curves were evaluated using the Kaplan-Meier analysis method. P-values <0.05 were considered statistically significant. All statistical analyses were performed using SPSS (SPSS 16.0 for Windows, Chicago, IL, USA).

Results

Patient characteristics

A total of 84 consecutive Stage III and IVA-B patients were treated with concurrent weekly chemoradiotherapy: 30 patients received docetaxel, and 54 patients received cisplatin. The characteristics of the 84 patients who completed the entire course of concurrent chemoradiotherapy are shown in Table 1.

Patient outcome

The median follow-up time for the entire group was 42.3 months (range, 8.6–50.8 months). The 3-year locoregional failure-free survival (LFS), distant failure-free survival (DFS), progression-free survival (PFS) and Overall survival (OS) rates for the whole group were 88.9%, 90.9%, 87.6% and 90.4%, respectively. In the subgroup analysis, there was no significant difference in the 3-year LFS (85.6% vs. 92.3%; p = 0.264), DFS (87.0% vs. 92.5%; p = 0.171), PFS (85.7% vs. 88.4%; p = 0.411; Figure 1) or OS (86.5% vs. 92.5%, p = 0 .298; Figure 2) of patients treated concurrently with docetaxel or cisplatin.

Toxicity

The planned program of 5-7 cycles of concurrent chemotherapy was completed by 26/30 (86.7%) and 43/54 (79.6%) of patients in the docetaxel and cisplatin group, respectively. Acute toxicities are summarized in Table 2. There were no cases of predominant neutrophil toxicity during the concurrent phase. Grade 1-2 vomiting (94% vs. 6%; p = 0.000) and grade 1-2 hemoglobin (85% vs. 43%; p = 0.000) toxicity were more common in the concurrent cisplatin group than the concurrent docetaxel group; however, grade 1-2 white blood cell count (WBC) toxicity was less common in the concurrent cisplatin group than the concurrent docetaxel group (53% vs. 74%; p = 0.000). In the concurrent docetaxel group, the predominant acute toxicity was mucositis, with 8/30 (26%) patients suffering from grade 3 mucotisis; however, we observed one grade 4 mucotisis in the concurrent cisplatin group (1/54; 1.9%).

Patterns of failure

Recurrence at the primary site was observed in 5/84 (5.9%) patients: 4/54 (7.4%) patients in concurrent cisplatin group and 1/30 (3.3%) patient in the concurrent docetaxel group. Cervical node recurrence was rare, and was only observed in 2/30 (6.7%) patients in the concurrent docetaxel group. Distant metastases occurred in a total of 10/84 (11.9%) patients. In the concurrent docetaxel group one patient had lung metastases, one patient had liver and lung metastases and two patients developed bone, liver and lung metastases. In concurrent cisplatin group, five patients had liver metastases and one patient developed lung metastases.

Discussion

Locoregionally advanced NPC is defined as a large primary nasopharyngeal mass and cervical node involvement without systemic metastases, and has a

very poor prognosis. In this study, 70% of the patients had locoregionally advanced Stage III and IVA-B disease at diagnosis. Treatment strategies for Stage III and IVA-B NPC patients rely on systematic therapies, including radiotherapy and chemotherapy. Chemotherapy combination schedules can be classified as induction, concurrent or adjuvant therapy. The landmark Intergroup 0099 (IG0099) study confirmed that concurrent cisplatin-based chemoradiotherapy followed by adjuvant PF (cisplatin plus 5-Fu) is the standard optimal treatment for locoregionally advanced NPC (Al-Sarraf et al., 1998). However, this result was not widely accepted by radiation oncologists in Asia, due to the pathological subtype of the patients recruited, and the poor outcome of the radiotherapy alone group. A series of phase III randomized trials have been conducted to confirm the efficacy of IG0099 (Lin et al., 2003; Lee et al., 2005; Wee et al., 2005). The role of induction and adjuvant chemotherapy in NPC remain controversial. Therefore, concurrent chemotherapy is widely accepted at our institution for Stage III and IVA-B NPC patients, with the selection of adjuvant or induction therapy based on clinical considerations.

To our knowledge, the optimal concurrent chemotherapy regimen during radiotherapy for locoregionally advanced NPC has not yet been established. Cisplatin is the most widely used chemotherapeutic agent in advanced NPC. Weekly concurrent doses of cisplatin (40 mg/m^2/week) were first introduced by Chan et al. (2005); however, only 78% of patients completed at least four cycles of chemotherapy. We modified the cisplatin dose to 30 mg/m^2 per week, using a concurrent weekly dose for ease of administration, and obtained tolerable toxicities. However, cisplatin-associated toxicities such as renal toxicity, ototoxicity and vomiting generally limit the use of cisplatin. Taxanes (docetaxel and paclitaxel) are newer cytotoxic agents which act via a different mechanism to cisplatin. Preclinical research data has demonstrated that docetaxel enhances tubulin polymerization and inhibits microtubule depolymerization, leading to cell-cycle blockade at the G2 phase. Docetaxel also enhances tissue oxygenation and induces apoptosis, contributing to a radiosensitizing effect (Tishler et al., 1992; Wahl et al., 1996; Tishler et al., 2002). Docetaxel has been combined with radiotherapy for the clinical treatment of many solid malignancies including SCCHN. Phase I/II studies of concurrent weekly taxane-based chemoradiotherapy in SCCHN have reported, encouraging preliminary results. Tishler et al. (Tishler et al., 2006) conducted a Phase II trial of concurrent weekly 20-30 mg/m^2 docetaxel with radiotherapy at 68-72 Gy in advanced head and neck cancer, and obtained a 2-year event free survival rate of 65%. In another Phase II trial conduced by Calais et al. (2004), patients with Stage III and IV oropharyngeal carcinoma received concurrent weekly 20 mg/m^2 docetaxel and radiotherapy at 70 Gy, leading to a local regional control rate (LRC) of 64%, and 3-year DFS and 3-year OS rates of 39% and 47%, respectively. Fukada et al. (2010) reported a trial of concurrent weekly low-dose (10 mg/m^2) docetaxel and radiotherapy at 60 Gy in Stage III/IV oropharyngeal and hypopharyngeal carcinoma, which obtained 3-year DFS, LRC and OS rates of 45%, 52% and 59%, respectively.

Studies of combined current taxane-based chemotherapy with radiation in NPC are limited. A Phase I trial of concurrent paclitaxel chemoradiotherapy in advanced NPC has been reported; however, the recommended dose was unclear (Chen et al., 2004). Hu et al. conducted a study using concurrent weekly paclitaxel (35 mg/m^2) followed by adjuvant chemotherapy in locally advanced NPC. The 3-year local regional control, progression-free survival and overall survival rates were 86%, 69% and 76%, respectively (Hu et al., 2009). In this study, we retrospectively compared the efficacy of concurrent cisplatin-based and docetaxel-based concurrent chemoradiotherapy in patients with Stage III and IVA-B NPC. There was no significant difference in the outcome of the two groups, with 3-year PFS, DFS and OS rates of 88.4%, 92.5% and 92.5% in the concurrent cisplatin group, and 85.7%, 87.0% and 86.5%, in the concurrent docetaxel group, respectively. The PFS and OS curves of the concurrent docetaxel group indicated a non-significant survival advantage ($p = 0.411$ and 0.298, respectively) over concurrent cisplatin (Fig. 1 and Fig. 2); however, it should be noted that 63.3% (19/30) of the patients in the concurrent docetaxel group had N2-3 disease compared to 44.4% (24/54) in the concurrent cisplatin group ($p = 0.336$). Recent data has supported the hypothesis that local control can be improved by intensity-modulated radiotherapy (IMRT); however, advanced N stage disease was still associated with a poorer overall survival (Lai et al., 2011). Docetaxel-based induction chemotherapy may provide a survival benefit for NPC patients with advanced stage disease, especially advanced N stage disease. Two Phase III trials (TAX323 and TAX324) showed that induction chemotherapy, which added docetaxel to cisplatin plus fluorouracil, significantly improved survival in head and neck cancer (Posner et al., 2007; Vermorken et al., 2007), and a Phase II trial in NPC using this strategy was reported by Hui et al. (2009) in Hong Kong, which obtained a survival advantage in the neoadjuvant docetaxel and cisplatin group compared to the concurrent cisplatin group.

Previous studies have demonstrated that hematological toxicities and mucosal toxicity are the most common limiting factors in taxane-based chemoradiotherapy. In the present study, acute mucosal toxicity was more common in the concurrent docetaxel group. Calais et al. (2004) reported that grade 3 and 4 mucositis occurred in 84% stage III oropharyngeal carcinoma patients receiving weekly docetaxel chemoradiotherapy, whereas grade 3 and 4 neutropenia were not common (5%). In this study 8/30 (26%) of the patients in the concurrent docetaxel group suffered grade 3 mucositis. Hu et al. (2009) reported that grade 2 and 3 acute mucosal toxicity occurred in 51% and 20% stage III and IV NPC patients receiving weekly paclitaxel. Grade 2 acute neutropenia toxicity occurring in 4% of the patients and no grade 3 toxicity observed during the concurrent phase. Using weekly low-dose docetaxel, Fukada et al. (2010) observed grade 3 mucositis and dermatitis in 44% and 17% locally advanced oropharyngeal or hypopharyngeal carcinoma patients, respectively, with only one patient suffering grade

4 pharyngeal edema and 3% of the patients suffering grade 3 or higher hematological toxicity. In this study, severe hematological toxicity was rare, and we did not observe any grade 3-4 neutropenia toxicity in the concurrent docetaxel group.

As this is a retrospective study, the T stage distribution of the two groups was not balanced (p = 0.038) and the dose delivered to the primary site of the concurrent cisplatin group was higher than the concurrent docetaxel group (p = 0.032); however, there was no difference in the TNM stage distribution of either treatment group. The aim of this study was to compare weekly docetaxel with standard cisplatin chemotherapy, to identify if alternative concurrent chemotherapy agents can provide additional benefits in terms of reduced toxicity and improved treatment outcomes. Based on the results, we suggest that a speculative trial comparing docetaxel with cisplatin in combination with radical radiation therapy should be conducted in patients with locoregionally advanced NPC.

In conclusion, this study demonstrates that a weekly concurrent docetaxel chemotherapy regimen, in combination with radiotherapy, is effective for patients with locoregionally advanced NPC. Further studies are required to fully compare the treatment outcomes and toxicities of docetaxel-based chemotherapy with standard cisplatin-based chemotherapy in patients with locoregionally advanced NPC receiving radiotherapy.

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The author(s) declare that they have no competing interests.

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